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(54) Title: COMPOSITIONS AND METHODS FOR DIAGNOSING AND TREATING CONDITIONS, DISORDERS, OR DISEASES INVOLVING CELL DEATH

tgcacccagc	cytcgcggga	ogcgtgggta	ggactttgaa	gaatacagtt	tcagtgaggt	60
aaactatttt	ttgtgatctg	ttacttata	ttactctgac	tttaacatt	ttttagcata	120
agaaaatagt	aaaaaaatat	tttaagtata	taaaatccct	ggctgctagc	taggagtcgc	180
ttgtgctat	agtgaanaaa	catggagact	ggagagctgt	tgatctattt	tcaccagtaa	240
ctgggtgact	ttaaaagggc	tgtaacttgt	actgtctcac	ttttatccag	ttctacactg	300
aaagattgtt	tttgatgatt	ctcaacatct	ttttctgcta	tgtaagactt	tcctcatgaa	360
attcagaacn	ttgccaattt	aggaatggca	aagatttttt	ccctaagttt	aaaagatcaa	420
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actatttct	cttccagggc	ttctattctg	ggttgggaga	atgctgttcc	agcaaccaagc	1560
agtgtgggta	tatatattca	taccaaagag	gcaatttgat	tgctcttggg	gttacaaaaa	1620
accaaatgtc	aatgcctgat	tagggaaatc	ascaataaaa	gtaaaaataa	tttagggata	1680
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gagaagatgg	aagtggttgg	ggaaacgtaa	taaaaaaaa	aaaaaagggc	ggcc	1794

(57) Abstract: The present invention relates to compositions and methods for the treatment and diagnosis of conditions, disorders, or diseases involving cell death. The invention encompasses protective nucleic acids which, when introduced into a cell predisposed to undergo cell death prevent, delay, or rescue the cell from death relative to a corresponding cell into which no exogenous nucleic acids have been introduced. The invention also encompasses novel protective sequence products, including proteins, polypeptides and peptides containing amino acid sequences of the proteins, fusion proteins, polypeptides and peptides, and antibodies directed against such gene products. The present invention also relates to methods and compositions for the diagnosis and treatment of conditions, disorders, or diseases, involving cell death.



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**COMPOSITIONS AND METHODS FOR DIAGNOSING AND TREATING
CONDITIONS, DISORDERS, OR DISEASES INVOLVING CELL DEATH**

5 1 **INTRODUCTION**

 The present invention relates to compositions and methods for the treatment and diagnosis of conditions, disorders, or diseases involving cell death, including, but not limited to, neurological disorders such as stroke. Nucleic acids are described herein which, when introduced into a cell either predisposed to undergo cell death or in the process of
10 undergoing cell death, prevent, delay, or rescue the cell from death relative to a corresponding cell into which no exogenous nucleic acids have been introduced. Such nucleic acids are referred to as "protective sequences". Protective sequences or their products are identified by their ability to prevent, delay, or rescue a cell, cells, tissues, organs, or organisms from dying. Protective sequences or their products are also identified via their ability to interact with other
15 genes or gene products involved in conditions or disorders involving cell death.

 The invention further includes recombinant DNA molecules and cloning vectors comprising protective sequences, and host cells and host organisms engineered to contain such DNA molecules and cloning vectors. The present invention further relates to protective sequence products and to antibodies directed against such protective sequence
20 products.

 The protective sequences identified, their products, or antibodies may be used diagnostically, prophylactically, therapeutically or as targets for therapeutic intervention. In this regard, the present invention provides methods for the identification and prophylactic or therapeutic use of compounds in the treatment and diagnosis of conditions, disorders, or
25 diseases involving cell death. Additionally, methods are provided for the diagnostic monitoring of patients undergoing clinical evaluation for the treatment of conditions or disorders involving cell death, for monitoring the efficacy of compounds in clinical trials and for identifying subjects who may be predisposed to such conditions, disorders, or diseases involving cell death.

30

2 **BACKGROUND OF THE INVENTION**

2.1 **Mechanisms which Lead to Cell Death**

It is widely recognized that at least two distinct cell death mechanisms exist for mammalian cells. These two mechanisms are necrosis and apoptosis, and are significant components of numerous conditions, disorders and disease states.

Necrosis plays an important physiologic role in signaling the presence of certain conditions. When cells die as a result of necrosis, the dying cells release substances that activate the body's immune response in a local, and in some cases widespread, reaction to the necrosis-inducing condition. This response is important in, for example, bacterial infection.

Experimental evidence in a wide variety of cells throughout the body has revealed that every cell can initiate a program of self-destruction, called apoptosis. This program can be initiated by a wide variety of natural and unnatural events. There are at least four distinct pathways for executing this program of cell death, and it is virtually certain that dozens, if not hundreds, of different intracellular biochemical cascades interact with each pathway. It is equally likely that certain cell types, such as cells in the heart or neurons, will utilize specialized signaling pathways that are not generally represented elsewhere in the body. However, since cell death is neither always necessary nor desired, it would be desirable to manipulate the manner in which cells start their death process. In some circumstances, preventing, delaying, or rescuing cells from death would either alleviate the disease or allow more time for definitive treatment to be administered to the patient. An example of this situation is brain cell death caused by ischemic stroke: preventing, delaying, or rescuing cells from death until the blood supply to the brain could be restored would greatly reduce, if not eliminate, the possibility of a person's death and/or long-term disability from stroke (Lee JM, et al. *Nature* 1999, 399(supp): A7-A14; Tarkowski E, et al. *Stroke* 1999, 30(2): 321-7; Pulera MR, et al. *Stroke* 1998, 29(12): 2622-30). In still other circumstances, the failure of cells to die may itself lead to disease such as cancer (Hetts SW. *JAMA* 1998, 297(4): 300-7).

Cell death plays an important role in the normal function of mammalian organisms. While it may seem counterintuitive for cells to have death as a normal part of their life cycle, controlled and physiologically appropriate cell death is important in regulating both the absolute and relative numbers of cells of a specific type. (Hetts SW. *JAMA* 1998, 297(4):

300-7; Garcia I, et al. *Science* 1992, 258(5080): 302-4). When the mechanism of apoptosis does not function properly and normal cell death does not occur, the resulting disease is characterized by unregulated cellular proliferation, as occurs in a neoplastic disease or an autoimmune disease (Hetts SW. *JAMA* 1998, 297(4): 300-7; Yachida M, et al. *Clin Exp Immunol* 1999, 116(1): 140-5).

One method for regulating cell death involves manipulating the threshold at which the process of cell death begins. This threshold varies significantly by cell type, tissue type, the type of injury or insult suffered by the cell, cellular maturity, and the physiologic conditions in the cell's environment (Steller H., *Science* 1995, 267(5203): 1445-9). Although it is probable that certain cellular injuries or insults irrevocably induce death, lesser injuries or insults may begin the dying process without inducing irreversible cell death. What constitutes a lesser injury or insult may vary tremendously with changes in the factors influencing that cell's death threshold. The ability to alter a cell's threshold for responding to an injury or insult, that is, to either promote or discourage cell death, would be a desirable goal for the treatment of conditions involving cell death. The ability to better control cell death, by either discouraging or promoting the mechanisms of cell death, would be an important invention for ameliorating disease (US Patents 5,925,640; 5,786,173; 5,858,715; 5,856,171).

Recent evidence suggests that the mechanisms of cellular death may be more complex than the two discrete pathways of apoptosis and necrosis. Examples of this evidence may be found in the central nervous system (CNS). In the complex CNS cellular environment, both necrosis and apoptosis are observed with commonly studied conditions, disorders, or diseases such as focal ischemia, global ischemia, toxic insults, prolonged seizures, excitotoxicity, and traumatic brain injury. In some reports, both apoptosis and necrosis have been described (Choi WS, et al. *J Neurosci Res* 1999, 57(1): 86-94; Li Y, et al. *J Neurol Sci* 1998, 156(2): 119-32; Lee J-M, et al. *Nature* 1999, 399(supp): A8-A14; Baumgartner WA, et al. *Ann Thorac Surg* 1999, 67(6): 1871-3; Fujikawa DG, et al. *Eur J Neurosci* 1999, 11(5): 1605-14; Gwag BJ, et al. *Neuroscience* 1999, 90(4): 1339-48; Mitchell II, et al. 1998, 84(2): 489-501; Nakashima K, et al. *J Neurotrauma* 1999, 16(2): 143-51; Ginsburg, MD *Cerebrovascular Disease: Pathophysiology, Diagnosis, and Management* 1998 Ch 42; Rink AD, et al. *Soc Neurosci Abstr* 1994, 20:250(Abstract)). Similar observations also occurred with brain tumor cells. (Maurer BJ, et al. *J Natl Cancer Inst* 1999, 91(13): 1138-46)

Other investigators found that neurons die by either apoptosis or necrosis under different environmental conditions (Taylor DL, et al. *Brain Pathol* 1999, 9(1): 93-117). There also are reports of a unique type of neuronal cell death following stroke. This new type of cell death has features common to both necrosis and apoptosis (Fukuda T, et al. *Neurosci Res* 1999, 33(1): 49-55). Other investigators believe that neuronal cell death is best represented by a continuum between apoptosis and necrosis, possibly mediated by calcium levels (Lee J-M, et al. 1999, 399(supp): A7-A14), or a combination of direct ischemic damage followed by indirect damage from excitotoxicity and loss of interneuronal connections (Martin LJ, et al. *Brain Res Bull* 1998, 46(4): 281-309). Further complicating the picture of neuronal cell death is the observation that the death of one or more neurons in one region of the brain can induce the death of neurons in other brain regions. This phenomenon has been observed with stroke as described above (Martin LJ, et al. *Brain Res Bull* 1998, 46(4): 281-309) as well as neuronal cell death induced by the withdrawal of growth factors (Ryu BR, et al. *J Neurobiol* 1999, 39(4): 536-46). Given the complex nature of actions and interactions among the many physiologic and molecular forces in brain tissue, and the different abilities of many substances acting either alone or in combination to induce cellular injury or death, it is difficult to determine with any degree of certainty if a nerve cell death process is due to apoptosis or necrosis (Graham DI, *Greenfield's Neuropathology* Ch 3 1997).

Despite the challenges in classifying the mechanism of cellular death, there is broad agreement that most, if not all, cells share common features in their death mechanisms: (see, e.g., Lee J.M., et al., *Nature* 1999, 399 (supp): A7-A14).

2.2 Selected Factors and Conditions which Inhibit Cell Death Mechanisms

Several factors have been reported to inhibit the cell death pathway. One of the best-known factors is the gene product *bcl-2* (Adams JM, et al. *Science* 1998, 281(5381): 1322-6; Vaux DL, et al. *Proc Natl Acad Sci* 1993, 90(3): 786-9; US Patent 5,856,171 and references cited therein). Expression of *bcl-2* is believed to regulate apoptotic death in neurons, kidney, heart, liver, blood and skin cells under experimental conditions. In addition to regulating death by apoptosis, *bcl-2* is believed to regulate death caused by non-apoptotic mechanisms. Factors related to *bcl-2* have been shown to be over-expressed in cancer and autoimmune conditions, disorders, or diseases (US Patent 5,856,171 and references cited

therein). Other related factors acting on the same pathway as *bcl-2* also delay or prevent cell death.

In the brain, several factors have been shown to influence the cell death pathway. In excitotoxic injury to neurons, it was shown that lithium or *bcl-2* each individually protected neurons against cell death (Nonaka S, et al. *Proc Natl Acad Sci* 1998, 95(5): 2642-7; Behl C, et al. *Biochem Biophys Res Commun* 1993, 197(2): 949-56). During ischemic injury to neurons, it was shown that nerve growth factor (NGF) and *bcl-2* individually offered protection against neuronal death (Guegan C, et al. *Neurobiol Dis* 1999, 6(3): 180-9; Linnik MD, et al. *Stroke* 1995, 26(9): 1670-4).

Factors acting to prevent cell death do not act solely in the brain. In the heart, increased tolerance to non-lethal ischemic injury was associated with an increased expression of the *bcl-2* gene, suggesting that *bcl-2* was involved in protecting the cardiac muscle cells against ischemic injury (Maulik N, et al. *Ann NY Acad Sci* 1999, 874:401-11). This same study demonstrated that lower levels of *bcl-2* expression were associated with higher rates of cardiac cell death. A similar result was found for mechanical injury to heart papillary muscle cells.

Recently, it has been demonstrated that *bcl-2* prevented cell death in a brain ischemia model (Guegan C, et al. *Neurobiol Dis* 1999, 6(3): 180-9; Linnik MD, et al. *Stroke* 1995, 26(9): 1670-4). It was shown that the activity of *bcl-2* to prevent neuronal death was consistently demonstrated across several different physiologic insults. It also has been demonstrated that the distinction between apoptotic death and necrotic death is open to question, so the possibility exists that *bcl-2* can prevent or delay the necrotic cell death pathway, the apoptotic cell death pathway or perhaps an as yet undemonstrated cell death pathway.

Preventing cell death is an important medical goal. Several types of mammalian cells, most notably neurons and cardiac muscle cells, have limited if any capacity to regenerate. Preventing the death of these cells from conditions such as heart attack, stroke, shock, infection, cancer, Alzheimer's disease or traumatic injury, to name a few, would be an important medical advance as the heart and brain cannot grow sufficient cells to replace those cells lost to disease or infection.

In addition to preventing cell death, delaying and/or rescuing cells from programmed cell death is also an important medical goal. In many pathological conditions where there is an expectation that the disease will be successfully treated, such as many types of infection, hypoxia, ischemia or metabolic disturbances, delaying cell death would allow the pathological condition to be treated without permanent damage to the cells. In other words, the cells may be put into a suspended state from which they could successfully be rescued and emerge with their normal function intact.

3 SUMMARY OF THE INVENTION

The present invention relates to the discovery, identification and characterization of protective sequences and to compositions and methods for the treatment and diagnosis of conditions, disorders, or diseases involving cell death. Protective sequences refer to nucleic acid molecules comprising nucleic acid sequences which, when introduced into a cell either predisposed to undergo cell death or in the process of undergoing cell death, prevent, delay, or rescue the cell from death relative to a corresponding cell into which no exogenous nucleic acids have been introduced. For example, protective sequences may act to prevent, delay, ameliorate, inhibit, reduce, or rescue neuronal cell death (*e.g.* apoptosis, necrosis and related cellular events). The invention further relates to the discovery, identification and characterization of gene products encoded by such nucleic acid molecules, or by degenerate, *e.g.*, allelic or homologous, variants thereof. Protective sequences also can be regulatory nucleic acids. Protective sequences further can be both coding sequences and regulatory sequences.

The invention further relates to target sequences. Target sequences include, but are not limited to, upstream and downstream regulatory sequences, upstream and downstream complete or partial gene or gene product sequences, antibodies, antisense molecules or sequences, ribozyme molecules, and other inhibitors or modulators directed against such protective sequences and protective sequence products.

Protective sequences and protective sequence products can be utilized prophylactically and/or therapeutically to prevent, delay ameliorate, inhibit, reduce, or rescue conditions of cell death or symptoms of conditions, disorders, or diseases involving cell death. The modulation of the expression of protective sequences, *e.g.*, endogenous protective

sequences, and/or the activity of the protective sequence products, *e.g.*, endogenous protective sequence products, can also be utilized prophylactically or therapeutically to prevent, delay, ameliorate, inhibit, reduce, or rescue conditions of cell death or symptoms of conditions, disorders, or diseases involving cell death. Further, protective sequences and protective
5 sequence products can be used to diagnose individuals exhibiting or predisposed to such conditions, disorders, or diseases involving cell death.

The compositions of the present invention include, in particular, nucleic acid molecules which comprise the following sequences: (a) nucleic acids of protective sequences, as well as allelic variants, homologs, mutants and fragments thereof; (b) nucleic acids which
10 encode protective sequence products; (c) nucleic acids which encode protective sequence regulatory elements; (d) nucleic acids which encode fusion proteins comprising protective sequence products or one or more protective sequence product domains fused to a heterologous polypeptide; (e) nucleic acids which encode fusion proteins comprising protective sequence regulatory elements fused to a heterologous polypeptide; (f) nucleic acids
15 which hybridize to the above described sequences under highly stringent or moderately stringent conditions, including, but not limited to, human homologs; and (g) complementary (*e.g.*, antisense) nucleic acids of the sequences described in (a) through (f), above. The nucleic acid molecules of the invention include, but are not limited to, cDNA, genomic DNA (including non-expressed features such as introns) and RNA sequences.

20 The present invention also encompasses expression gene products of the protective sequences listed above; *i.e.*, proteins and/or polypeptides that are encoded by the above protective sequences. The present invention also encompasses expression gene products generated by differentially or alternately splicing the protective sequences listed above.

Nucleic acid molecules that can conceptually encode these differentially or alternately spliced

and ribozyme molecules, and gene or regulatory sequence replacement constructs, which can be used to modulate, inhibit or enhance expression of a protective sequence.

5 The present invention further encompasses cloning and expression vectors, which may include, but are not limited to, bacterial, fungal, insect, plant, and mammalian vectors, which contain the protective nucleic acid sequences of the invention, which can be used as probes or to express those protective nucleic acid sequences, protective sequence products, genes and/or gene products in host cells or organisms. The present invention also relates to cells that have been transformed, transfected, or infected with such vectors, and to cells engineered to contain or express the protective nucleic acid sequences, protective
10 sequence products, genes, gene products, and/or regulatory elements of the invention. Further, non-human host organisms which have been transformed, transfected, or infected with these protective nucleic acid sequences, or their regulatory elements, are also encompassed in the present invention. Host organisms of the invention include organisms transformed, transfected, or infected with the cloning vectors described above, including, but not limited to,
15 non-human transgenic animals, and particularly transgenic non-human mammals which have been engineered to express a protective sequence, protective sequence product, gene, gene product, or regulatory element of the invention, or "knock-outs" which have been engineered to not express the protective sequence, protective sequence product, gene, gene product, or regulatory element of the invention.

20 The transgenic animals of the invention include animals which express a mutant variant or polymorphism of a protective sequence, protective sequence product, gene, gene product, or regulatory element, particularly a mutant variant or polymorphism of a protective sequence, protective sequence product, gene, gene product, or regulatory element which is associated with a condition, disorder, or disease involving cell death. The transgenic
25 animals of the invention further include those that express a protective sequence transgene at higher or lower levels than normal. The transgenic animals of the invention further include those which express the protective sequence, protective sequence product, gene, gene product, or regulatory element in all their cells, "mosaic" animals which express the protective sequence, protective sequence product, gene, gene product, or regulatory element in only some
30 of their cells, and those in which the protective sequence, protective sequence product, gene, gene product, or regulatory element is selectively introduced into and expressed in a specific

cell type(s). The transgenic animals of the invention also include "knock-out" animals. Knock-out animals comprise animals that have been engineered to no longer express the protective sequence, protective sequence product, gene, gene product, or regulatory element.

5 The present invention also relates to methods and compositions for the diagnosis of conditions, disorders, or diseases involving cell death, as well as for the identification of subjects susceptible to such conditions, disorders, or diseases. Such methods comprise, for example, measuring expression of the protective sequence, protective sequence product, gene, gene product, or regulatory element in a patient sample, or detecting a mutation
10 in the protective sequence, protective sequence product, gene, gene product, or regulatory element in the genome of a mammal, including a human, suspected of exhibiting such a condition, disorder, or disease. The protective nucleic acid molecules of the invention can be used also as diagnostic hybridization probes, or as primers for diagnostic PCR analysis to identify protective sequences, protective sequence products, genes, gene products, or regulatory element mutations, allelic variations or regulatory defects, such as defects in the
15 expression of the protective sequence, protective sequence product, gene, gene product, or regulatory element. Such diagnostic PCR analyses can be used to diagnose individuals with a condition, disorder, or disease involving cell death associated with a particular protective sequence, protective sequence product, gene, gene product, or regulatory element mutation, allelic variation or regulatory defect. Such diagnostic PCR analyses can be used also to
20 identify individuals susceptible to such conditions, disorders, or diseases involving cell death.

Methods and compositions, including pharmaceutical compositions, for the treatment of conditions, disorders, or diseases involving cell death also are included in the invention. Such methods and compositions can increase, decrease or otherwise modulate the level of protective sequences, protective sequence products, genes, gene products, or their
25 regulatory elements in a patient in need of such treatment. Such methods and compositions can also modulate the level of protective sequence expression (*e.g.*, endogenous protective sequence expression) and/or the level of activity of a protective sequence product, (*e.g.*, endogenous protective sequence product). Further, since the protective sequence or protective sequence product need not normally be involved in such conditions, disorders, or diseases,
30 such methods include, for example, modulating the expression of the protective sequence and/or the activity of the protective sequence product for the treatment of conditions,

disorders, or diseases involving cell death which are normally mediated by some other gene.

In one embodiment, such methods and compositions are utilized for the treatment of the types of conditions, disorders, or diseases, which can be prevented, delayed or rescued from cell death and include, but are not limited to, those associated with the central nervous system including neurological and psychiatric conditions, disorders, or diseases; those of the peripheral nervous system; conditions, disorders, or diseases caused by physical injury; conditions, disorders, or diseases of the blood vessels or heart; conditions, disorders, or diseases of the respiratory system; neoplastic conditions, disorders, or diseases; conditions, disorders, or diseases of blood cells; conditions, disorders, or diseases of the gastrointestinal tract; conditions, disorders, or diseases of the liver; conditions, disorders, or diseases of the pancreas; conditions, disorders, or diseases of the kidney; conditions, disorders, or diseases of the ureters, urethra or bladder; conditions, disorders, or diseases of the male genital system; conditions, disorders, or diseases of the female genital tract; conditions, disorders, or diseases of the breast; conditions, disorders, or diseases of the endocrine system; conditions, disorders, or diseases of the thymus or pineal gland; conditions, disorders, or diseases of the skin or mucosa; conditions, disorders, or diseases of the musculoskeletal system; conditions, disorders, or diseases causing a fluid or hemodynamic derangement; inherited conditions, disorders, or diseases; conditions, disorders, or diseases of the immune system or spleen; conditions, disorders, or diseases caused by a nutritional disease; and conditions, disorders, or diseases typically occurring in infancy or childhood, as described in Section 5.4.1.1. below.

In yet another embodiment, the methods and compositions of the invention are utilized for the prevention, or delay, of cell death in the event of one or more infections which may be caused by bacteria; viruses; members of the family rickettsiae or chlamydia; fungi, yeast, hyphae or pseudohyphae; prions; protozoans; or metazoans.

In a further embodiment, the compounds and methods of the invention can be used to treat infections or conditions, disorders, or diseases which cause cell death in organ systems including, but not limited to, blood vessels, heart, red blood cells, white blood cells, lymph nodes, spleen, respiratory system, oral cavity, gastrointestinal tract, liver and biliary tract, pancreas, kidney, lower urinary tract, upper urinary tract and bladder, male sexual organs and genitalia, female sexual organs and genitalia, breast, thyroid gland, adrenal gland, parathyroid gland, skin, musculoskeletal system, bone marrow or bones.

In another embodiment, the compounds and methods of the invention can be used to treat further physiological impacts on organs caused by the infections which induce cell death including, but not limited to, fever equal to or greater than 101.5 degrees Fahrenheit, a decrease or increase in pulse rate by more than 20 beats per minute, a decrease
5 or increase in supine systolic blood pressure by more than 30 millimeters of mercury, an increase or decrease in respiratory rate by more than 8 breaths per minute, an increase or decrease in blood pH by more than 0.10 pH units, an increase or decrease in one or more serum electrolytes outside of the clinical laboratory's usual reference range, an increase or decrease in the partial pressure of arterial oxygen or carbon dioxide outside of the clinical
10 laboratory's usual reference range, an increase or decrease in white or red blood cells outside of the laboratory's usual reference range, an acute confusional state such as delirium where delirium is defined by the American Psychiatric Association's DSM-IV Manual or a diminished level of consciousness or attention.

In another embodiment, the compounds and methods of the invention can be
15 used to promote cell death. These compounds could be useful for treating and/or ameliorating conditions caused by, for example, cancer and autoimmune diseases, both of which are manifested by an uncontrolled growth of cells.

The invention still further relates to methods for identifying compounds which modulate the expression of a protective sequence and/or the synthesis or activity of a
20 protective sequence product. Such compounds include therapeutic compounds which can be used as pharmaceutical compositions to reduce or eliminate the symptoms of conditions, disorders, or diseases involving cell death. Cellular and non-cellular assays are described which can be used to identify compounds which interact with a protective sequence, protective sequence product, gene, gene product, and/or regulatory element, *e.g.*, modulate the
25 activity of a protective sequence and/or bind to a protective sequence product. Such cell-based assays of the invention utilize cells, cell lines, or engineered cells or cell lines that express the protective sequence, protective sequence product, gene, gene product, and/or regulatory element.

In one embodiment, such methods comprise contacting a compound to a cell
30 which expresses a protective sequence, protective sequence product, gene, gene product, and/or regulatory element, measuring the level of protective sequence expression, gene

product expression or gene product activity, and comparing this level to the level of protective sequence expression, gene product expression or gene product activity produced by the cell in the absence of the compound, such that if the level obtained in the presence of the compound differs from that obtained in its absence, a compound which modulates the expression of the protective sequence and/or the synthesis or activity of protective sequence products has been identified.

In an alternative embodiment, such methods comprise administering a compound to a host, *e.g.*, a transgenic animal which expresses a protective sequence transgene or a mutant protective sequence transgene, and measuring the level of protective sequence expression, gene product expression or gene product activity. The measured level is compared to the level of protective sequence expression, gene product expression or gene product activity in a host which is not exposed to the compound, such that if the level obtained when the host is exposed to the compound differs from that obtained when the host is not exposed to the compound, a compound which modulates the expression of the protective sequence and/or the synthesis or activity of protective sequence products, and/or the symptoms of conditions, disorders, or diseases involving cell death, has been identified.

3.1 Definitions

"Protective sequence", as used herein, refers to nucleic acid molecules comprising nucleic acid sequences which, when introduced into a cell predisposed to either undergo cell death or in the process of undergoing cell death, prevent, delay, or rescue the cell from death relative to a corresponding cell into which no exogenous protective nucleic acids have been introduced. In one embodiment, a protective sequence encodes a protective sequence product. In another embodiment, protective sequences are any transcriptional products of the sequences disclosed herein. In another embodiment, protective sequences comprise regulatory elements of the sequences disclosed herein which modulate the expression of a nucleic acid within a cell. For example, protective sequences, their products, or their regulatory elements may act to prevent, delay, or rescue a cell, cells, tissues, organs, or organisms from dying. Compounds which modulate protective sequence expression or activity of the protective sequence product can be used in the treatment of conditions, disorders or diseases associated with cell death processes. It is to be understood that the

protective sequences described above can act to ameliorate or delay symptoms related to cell death. Although the protective sequences may be involved directly in such cell death related conditions or disorders, in certain cases, the protective sequences will not normally be involved in such conditions or disorders, but will be effective for the treatment and/or prevention of such disorders. In these cases, modulation of the expression of the protective sequence and/or the activity of the protective sequence product will be useful for the treatment of conditions, disorders, or diseases involving cell death which are normally mediated by some other gene.

"Cell death", as used herein, refers to any mechanism and/or pathway whereby a cell undergoes a series of events which ultimately would lead to the death of the cell. For example, cell death may be caused by various processes including, but not limited to, apoptosis or programmed cell death, necrosis, or an as yet unidentified cell death pathway. Cell death may be induced in individual cells as a consequence of numerous internal and external stimuli including, but not limited to, genetic predisposition, toxic chemicals or processes, heat, cold, rapid environmental changes, radiation, viruses, prions, bacteria, disruption of nutrient balance, or exposure to bi-products and signaling from other cells undergoing cell death. The protective sequences disclosed herein, when introduced into a cell (*e.g.* a neuronal cell) which has undergone an event that would ultimately lead to cell death (*e.g.* ischemia), are capable of rescuing the cell from cell death. Moreover, when a protective sequence, in combination with a reporter gene (*e.g.* green fluorescent protein), is introduced into a cell which has undergone an event that would ultimately lead to cell death, expression of the reporter gene is an indication that the protective sequence is capable of rescuing the cell from cell death.

4 BRIEF DESCRIPTION OF THE FIGURES

Figures 1(A-J). Protective nucleic acids. See Table 1 for the identity, the sequence identifier number, the length in base pairs and the Accession Number for each of the sequences shown in these figures.

Figure 2. Restriction map and diagram of plasmid pCMV-SPORT2. This plasmid was used as the cloning vector for the protective sequences. Each clone was ligated

into the *SalI-NotI* restriction sites of the plasmid.

Figures 3(A- F). Protected Cortical Neurons Visualized by Detection of EGFP Expressing Cells. Figures 3A and 3B represent non-stroked, positive control samples. Figure 3C represents a positive control, stroked sample using Bcl-2. Figure 3D represents a stroked, negative control sample. Figure 3E represents a stroked sample protected by a representative protective sequence. Figure 3F presents the average number of neurons that survived for three days in both a stroked sample protected by a protective sequence and a corresponding stroked, negative control sample.

Figures 4(A-AB). Open Reading Frames for CNI-00718. This Figure depicts the 28 potential ORFs for CNI-00718. Also shown are the nucleotide sequences which encode the ORFs.

Figures 5(A-L). Open Reading Frames for CNI-00722. This Figure depicts the 12 potential ORFs for CNI-00722. Also shown are the nucleotide sequences which encode the ORFs.

Figures 6(A-K). Open Reading Frames for CNI-00725. This Figure depicts the 11 potential ORFs for CNI-00725. Also shown are the nucleotide sequences which encode the ORFs.

Figures 7(A-Z). Open Reading Frames for CNI-00726. This Figure depicts the 26 potential ORFs for CNI-00726. Also shown are the nucleotide sequences which encode the ORFs.

Figures 8(A-S). Open Reading Frames for CNI-00727. This Figure depicts the 19 potential ORFs for CNI-00727. Also shown are the nucleotide sequences which encode the ORFs.

Figures 9(A-X). Open Reading Frames for CNI-00728. This Figure depicts the 24 potential ORFs for CNI-00728. Also shown are the nucleotide sequences which encode the ORFs.

5 Figures 10(A-V). Open Reading Frames for CNI-00729. This Figure depicts the 22 potential ORFs for CNI-00729. Also shown are the nucleotide sequences which encode the ORFs.

10 Figures 11(A-I). Open Reading Frames for CNI-00730. This Figure depicts the 9 potential ORFs for CNI-00730. Also shown are the nucleotide sequences which encode the ORFs.

15 Figures 12(A-G). Open Reading Frames for CNI-00731. This Figure depicts the 7 potential ORFs for CNI-00731. Also shown are the nucleotide sequences which encode the ORFs.

20 Figures 13(A-H). Open Reading Frames for CNI-00732. This Figure depicts the 8 potential ORFs for CNI-00732. Also shown are the nucleotide sequences which encode the ORFs.

5 **DETAILED DESCRIPTION OF THE INVENTION**

Protective sequences of the invention are described herein. Also described are recombinant, cloned and degenerate variants, homologs, orthologs, mutants and fragments thereof. The compositions of the invention further include protective sequence products (*e.g.* proteins or RNA) which are encoded or produced by the nucleic acid molecules of the invention, and the modulation of protective sequence expression and/or gene product activity in the treatment of conditions, disorders, or diseases involving cell death. Further, antibodies directed against the protective sequence products, or conserved variants or fragments thereof, and viral-, cell-, plant-, and animal-based models by which the protective sequences may be further characterized and utilized are also discussed in this section.

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5.1 The Protective Sequences

The protective sequences of the invention are described in this section.

Specifically, these protective sequences have been shown to prevent, delay, or rescue cell death in a cell predisposed for undergoing cell death, whether the pathway that leads to the cell death involves apoptosis, necrosis or an as yet undefined pathway. The protective sequences, their SEQ ID NOS and additional information related to the protective sequences are listed below, in Table 1.

The protective sequences listed in Table 1 may be obtained using cloning methods well known to those skilled in the art, including but not limited to the use of appropriate probes to detect the protective sequences within an appropriate cDNA or gDNA (genomic DNA) library. (See, for example, Sambrook *et al.*, 1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratories, which is incorporated by reference herein in its entirety). Probes for the novel sequences reported herein may be obtained directly from CNI-NPP2-CP10, which represents a composite deposit containing the isolated clones, which was deposited with the ATCC as Accession No. PTA-1492 on March 16, 2000. Alternatively, oligonucleotide probes for the novel protective sequences may be synthesized based on the DNA sequences disclosed herein.

TABLE 1

PROTECTIVE SEQUENCES

<u>Protective sequence</u>	<u>SEQ ID NO:</u>	<u>Figure No.</u>	<u>Length (bp)</u> <u>(NotI-SalI fragment)</u>
CNI-00718	1	1A	1794
CNI-00722	58	1B	810
CNI-00725	83	1C	920
CNI-00726	106	1D	2144
CNI-00727	159	1E	1293
CNI-00728	198	1F	1466
CNI-00729	247	1G	1659
CNI-00730	292	1H	722
CNI-00731	311	1I	364
CNI-00732	326	1J	1046

The isolated protective nucleic acid molecules of the invention include, in particular, nucleic acid molecules which comprise the following sequences: (a) nucleic acids of protective sequences, as well as allelic variants, homologs, mutants and fragments thereof; (b) nucleic acids which encode protective sequence products and/or their regulatory elements, or fragments thereof; (c) nucleic acids which encode fusion proteins comprising protective sequence products and/or their regulatory elements, or one or more protective sequence product domains and/or their regulatory elements fused to a heterologous polypeptide; (d) nucleic acids which hybridize to the above described sequences under highly stringent or moderately stringent conditions, including, but not limited to human homologs; and (e) complementary (*e.g.*, antisense) nucleic acids of the sequences described in (a) through (d), above. The nucleic acid molecules of the invention include, but are not limited to, cDNA, genomic DNA and RNA sequences.

The nucleic acids of the invention also include nucleic acids which have at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or more nucleic acid identity to the protective nucleic acids of (a)-(d) above. The nucleic acids of the invention further include nucleic acids which encode polypeptides having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or higher amino acid sequence identity to the polypeptides encoded by the protective nucleic acids of (a)-(d).

To determine the percent identity of two amino acid sequences or of two nucleic acids, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % identity = # of identical overlapping positions/total # of positions x 100). In one embodiment, the two sequences are the same length.

The determination of percent identity between two sequences also can be accomplished using a mathematical algorithm. A preferred, non-limiting example of a

mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul (1990) *Proc. Natl. Acad. Sci. USA* 87:2264-2268, modified as in Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-410. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleic acids homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.* (1997) *Nucleic Acids Res.* 25:3389-3402. Alternatively, PSI-Blast can be used to perform an iterated search that detects distant relationships between molecules (*Id.*). When utilizing BLAST, Gapped BLAST and PSI-Blast programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used (see <http://www.ncbi.nlm.nih.gov>). Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, (1988) *CABIOS* 4:11-17. Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4 can be used.

The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, typically only exact matches are counted.

The nucleic acids of the invention further include: (a) any nucleic acid which hybridizes to a nucleic acid molecule of the invention under moderately stringent conditions, *e.g.*, hybridization to filter-bound DNA in 6x sodium chloride/sodium citrate (SSC) at about 45°C followed by one or more washes in 0.2xSSC/0.1% SDS at about 50-65°C, or (b) under highly stringent conditions, *e.g.*, hybridization to filter-bound nucleic acid in 6xSSC at about 45°C followed by one or more washes in 0.1xSSC/0.2% SDS at about 68°C, or under other hybridization conditions which are apparent to those of skill in the art (*see*, for example, Ausubel F.M. *et al.*, eds., 1989, *Current Protocols in Molecular Biology*, Vol. I, Green Publishing Associates, Inc., and John Wiley & sons, Inc., New York, at pp. 6.3.1-6.3.6 and

2.10.3). Preferably the nucleic acid molecule that hybridizes to the nucleic acid of (a) and (b), above, is one which comprises the complement of a nucleic acid molecule which encodes a protective sequence product. In a preferred embodiment, nucleic acid molecules comprising the nucleic acids of (a) and (b), above, encode protective sequence products.

5 Functionally equivalent protective sequence products include naturally occurring protective sequence products present in the same or different species. Functionally equivalent protective sequence products also include gene products which retain at least one of the biological activities of the protective sequence products, and/or which are recognized by and bind to antibodies (polyclonal or monoclonal) directed against the protective sequence
10 products.

 Among the nucleic acid molecules of the invention are deoxyoligonucleotides ("oligos") which hybridize under highly stringent or moderately stringent conditions to the nucleic acid molecules described above. In general, for probes between 14 and 70 nucleotides in length the melting temperature (T_m) is calculated using the formula: T_m
15 ($^{\circ}\text{C}$) = $81.5 + 16.6(\log[\text{monovalent cations (molar)}]) + 0.41 (\% \text{ G+C}) - (500/N)$ where N is the length of the probe. If the hybridization is carried out in a solution containing formamide, the melting temperature is calculated using the equation T_m ($^{\circ}\text{C}$) = $81.5 + 16.6(\log[\text{monovalent cations (molar)}]) + 0.41 (\% \text{ G+C}) - (0.61 \% \text{ formamide}) - (500/N)$ where N is the length of the probe. In general, hybridization is carried out at about 20-25 degrees below T_m (for DNA-
20 DNA hybrids) or 10-15 degrees below T_m (for RNA-DNA hybrids).

 Exemplary highly stringent conditions may refer, *e.g.*, to washing in 6xSSC/0.05% sodium pyrophosphate at 37°C (for about 14-base oligos), 48°C (for about 17-base oligos), 55°C (for about 20-base oligos) and 60°C (for about 23-base oligos).

 Fragments of the nucleic acid molecules can be at least 9 nucleotides in length.
25 Fragments of the nucleic acid molecules can refer also to exons or introns, and, further, can refer to portions of coding regions that encode domains of protective sequence products.

 The invention also encompasses (a) DNA vectors which contain any of the foregoing coding sequences and/or their complements (*i.e.*, antisense); (b) DNA expression vectors which contain any of the foregoing coding sequences operatively associated with a regulatory element which directs the expression of the coding sequences; and (c) genetically
30 engineered host cells which contain such vectors or have been engineered to contain and/or

express a nucleic acid sequence of the invention, *e.g.*, any of the foregoing coding sequences operatively associated with a regulatory element which directs the expression of the coding sequences in the host cell. As used herein, regulatory elements include but are not limited to inducible and non-inducible promoters, enhancers, operators and other elements known to those skilled in the art which drive and regulate expression. The invention further includes fragments of any of the DNA sequences disclosed herein.

The nucleic acid molecules may encode or act as antisense molecules, useful, for example, in protective sequence regulation, and/or as hybridization probes and/or as primers in amplification reactions of protective nucleic acid sequences. Further, such sequences may be used as part of ribozyme and/or triple helix sequences, also useful for protective sequence regulation. Still further, such molecules may be used as components of diagnostic methods whereby, for example, the presence of a particular allele involved in a condition, disorder, or disease involving cell death may be detected.

The protective nucleic acids of the invention can be readily obtained, for example, by standard sequencing and the sequences provided herein.

As will be appreciated by those skilled in the art, DNA sequence polymorphisms of a protective sequence will exist within a population of individual organisms (*e.g.*, within a human population). Such polymorphisms may exist, for example, among individuals within a population due to natural allelic variation. Such polymorphisms include ones that lead to changes in amino acid sequence. An allele is one of a group of alternative forms of a gene that occur at a given genetic locus.

As used herein, the phrase "allelic variant" refers to a nucleic acid that occurs at a given locus or to a gene product encoded by that nucleic acid. Such natural allelic variations can typically result in 1-5% variance in the nucleic acid of a given gene.

Sequencing the gene of interest in a number of different individuals can identify alternative alleles. Using hybridization probes to identify the same genetic locus in a variety of individuals can readily carry this out.

As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules comprising any of up to six open reading frames which may or may not encode a polypeptide of the invention. For example, the terms "gene" and "recombinant gene" refer to nucleic acid molecules encoding any of the open reading frames shown in Figures 4-13, and

described in Tables 2-11, respectively. The term can further include nucleic acid molecules comprising upstream and/or exon/intron sequences and structures.

TABLE 2**OPEN READING FRAMES FOR CNI-00718**

OPEN READING FRAME NUMBER	LENGTH	LOCATION	SEQUENCE ID. NO.
1	39 Nucleotide	202-240 of Seq. Id. No. 1	2
	12 Amino Acid		3
2	45 Nucleotide	315-359 of Seq. Id. No. 1	4
	14 Amino Acid		5
3	51 Nucleotide	356-406 of Seq. Id. No. 1	6
	16 Amino Acid		7
4	42 Nucleotide	385-426 of Seq. Id. No. 1	8
	13 Amino Acid		9
5	15 Nucleotide	423-437 of Seq. Id. No. 1	10
	4 Amino Acids		11
6	12 Nucleotide	467-478 of Seq. Id. No. 1	12
	3 Amino Acid		13
7	27 Nucleotide	483-509 of Seq. Id. No. 1	14
	8 Amino Acid		15
8	51 Nucleotide	597-647 of Seq. Id. No. 1	16
	16 Amino Acid		17
9	30 Nucleotide	685-714 of Seq. Id. No. 1	18
	9 Amino Acids		19
10	221 Nucleotide	704-925 of Seq. Id. No. 1	20
	73 Amino Acid		21
11	69 Nucleotide	715-783 of Seq. Id. No. 1	22
	22 Amino Acid		23
12	57 Nucleotide	727-783 of Seq. Id. No. 1	24
	18 Amino Acid		25
13	18 Nucleotide	735-752 of Seq. Id. No. 1	26
	5 Amino Acids		27
14	30 Nucleotide	891-920 of Seq. Id. No. 1	28
	9 Amino Acid		29
15	339 Nucleotide	954-1292 of Seq. Id. No. 1	30
	112 Amino Acid		31
16	63 Nucleotide	997-1059 of Seq. Id. No. 1	32
	20 Amino Acid		33
17	207 Nucleotide	1086-1292 of Seq. Id. No. 1	34
	68 Amino Acids		35
18	72 Nucleotide	1221-1292 of Seq. Id. No. 1	36
	23 Amino Acid		37
19	24 Nucleotide	1335-1358 of Seq. Id. No. 1	38
	7 Amino Acid		39

20	21 Nucleotide	1367-1387 of Seq. Id. No. 1	40
	6 Amino Acid		41
21	36 Nucleotide	1439-1474 of Seq. Id. No. 1	42
	11 Amino Acids		43
22	183 Nucleotide	1461-1643 of Seq. Id. No. 1	44
	60 Amino Acid		45
23	99 Nucleotide	1541-1639 of Seq. Id. No. 1	46
	32 Amino Acid		47
24	18 Nucleotide	1626-1643 of Seq. Id. No. 1	48
	5 Amino Acid		49
25	12 Nucleotide	1632-1643 of Seq. Id. No. 1	50
	3 Amino Acids		51
26	21 Nucleotide	1684-1704 of Seq. Id. No. 1	52
	6 Amino Acid		53
27	18 Nucleotide	1725-1742 of Seq. Id. No. 1	54
	5 Amino Acids		55
28	27 Nucleotide	1747-1773 of Seq. Id. No. 1	56
	8 Amino Acids		57

TABLE 3**OPEN READING FRAMES FOR CNI-00722**

OPEN READING FRAME NUMBER	LENGTH	LOCATION	SEQUENCE ID. NO.
1	15 Nucleotide	242-256 of Seq. Id. No. 58	59
	4 Amino Acid		60
2	27 Nucleotide	301-327 of Seq. Id. No. 58	61
	8 Amino Acid		62
3	12 Nucleotide	316-327 of Seq. Id. No. 58	63
	3 Amino Acid		64
4	51 Nucleotide	385-435 of Seq. Id. No. 58	65
	16 Amino Acid		66
5	33 Nucleotide	446-478 of Seq. Id. No. 58	67
	10 Amino Acid		68
6	15 Nucleotide	478-492 of Seq. Id. No. 58	69
	4 Amino Acid		70
7	135 Nucleotide	498-632 of Seq. Id. No. 58	71
	44 Amino Acid		72
8	57 Nucleotide	576-632 of Seq. Id. No. 58	73
	18 Amino Acid		74
9	96 Nucleotide	632-727 of Seq. Id. No. 58	75
	31 Amino Acid		76
10	93 Nucleotide	635-727 of Seq. Id. No. 58	77
	30 Amino Acid		78
11	51 Nucleotide	714-764 of Seq. Id. No. 58	79
	16 Amino Acids		80
12	57 Nucleotide	754-810 of Seq. Id. No. 58	81
	19 Amino Acids		82

TABLE 4**OPEN READING FRAMES FOR CNI-00725**

5	OPEN READING FRAME NUMBER	LENGTH	LOCATION	SEQUENCE ID. NO.
10	1	21 Nucleotide 6 Amino Acid	67-87 of Seq. Id. No. 83	84 85
	2	39 Nucleotide 12 Amino Acid	187-225 of Seq. Id. No. 83	86 87
	3	48 Nucleotide 15 Amino Acid	258-305 of Seq. Id. No. 83	88 89
15	4	75 Nucleotide 24 Amino Acid	262-336 of Seq. Id. No. 83	90 91
	5	99 Nucleotide 32 Amino Acids	333-431 of Seq. Id. No. 83	92 93
20	6	12 Nucleotide 3 Amino Acid	359-370 of Seq. Id. No. 83	94 95
	7	54 Nucleotide 17 Amino Acid	378-431 of Seq. Id. No. 83	96 97
	8	45 Nucleotide 14 Amino Acids	482-526 of Seq. Id. No. 83	98 99
25	9	63 Nucleotide 20 Amino Acid	619-681 of Seq. Id. No. 83	100 101
	10	42 Nucleotide 13 Amino Acids	640-681 of Seq. Id. No. 83	102 103
30	11	116 Nucleotide 38 Amino Acids	805-920 of Seq. Id. No. 83	104 105

TABLE 5**OPEN READING FRAMES FOR CNI-00726**

OPEN READING FRAME NUMBER	LENGTH	LOCATION	SEQUENCE ID. NO.
1	444 Nucleotide	23-466 of Seq. Id. No. 106	107
	147 Amino Acid		108
2	24 Nucleotide	111-134 of Seq. Id. No. 106	109
	7 Amino Acid		110
3	15 Nucleotide	138-152 of Seq. Id. No. 106	111
	4 Amino Acid		112
4	318 Nucleotide	149-466 of Seq. Id. No. 106	113
	105 Amino Acid		114
5	42 Nucleotide	163-204 of Seq. Id. No. 106	115
	13 Amino Acids		116
6	294 Nucleotide	173-466 of Seq. Id. No. 106	117
	97 Amino Acid		118
7	30 Nucleotide	201-230 of Seq. Id. No. 106	119
	9 Amino Acid		120
8	12 Nucleotide	232-243 of Seq. Id. No. 106	121
	3 Amino Acid		122
9	177 Nucleotide	290-466 of Seq. Id. No. 106	123
	58 Amino Acids		124
10	36 Nucleotide	312-347 of Seq. Id. No. 106	125
	11 Amino Acids		126
11	18 Nucleotide	352-369 of Seq. Id. No. 106	127
	5 Amino Acid		128
12	63 Nucleotide	404-466 of Seq. Id. No. 106	129
	20 Amino Acid		130
13	60 Nucleotide	407-466 of Seq. Id. No. 106	131
	19 Amino Acid		132
14	45 Nucleotide	422-466 of Seq. Id. No. 106	133
	14 Amino Acids		134
15	27 Nucleotide	624-650 of Seq. Id. No. 106	135
	8 Amino Acids		136
16	72 Nucleotide	1006-1077 of Seq. Id. No. 106	137
	23 Amino Acid		138
17	57 Nucleotide	1224-1280 of Seq. Id. No. 106	139
	18 Amino Acid		140
18	48 Nucleotide	1335-1382 of Seq. Id. No. 106	141
	15 Amino Acid		142

19	15 Nucleotide	1382-1396 of Seq. Id. No. 106	143
	4 Amino Acids		144
20	78 Nucleotide	1492-1569 of Seq. Id. No. 106	145
	25 Amino Acid		146
21	33 Nucleotide	1514-1546 of Seq. Id. No. 106	147
	10 Amino Acid		148
22	156 Nucleotide	1670-1825 of Seq. Id. No. 106	149
	51 Amino Acid		150
23	30 Nucleotide	1819-1848 of Seq. Id. No. 106	151
	9 Amino Acids		152
24	69 Nucleotide	1827-1895 of Seq. Id. No. 106	153
	22 Amino Acids		154
25	63 Nucleotide	1833-1895 of Seq. Id. No. 106	155
	20 Amino Acids		156
26	66 Nucleotide	1951-2016 of Seq. Id. No. 106	157
	21 Amino Acids		158

TABLE 6**OPEN READING FRAMES FOR CNI-00727**

5	OPEN READING FRAME NUMBER	LENGTH	LOCATION	SEQUENCE ID. NO.
10	1	45 Nucleotide	237-281 of Seq. Id. No. 159	160
		14 Amino Acid		161
	2	27 Nucleotide	255-281 of Seq. Id. No. 159	162
		8 Amino Acid		163
	3	12 Nucleotide	395-406 of Seq. Id. No. 159	164
15		3 Amino Acid		165
	4	45 Nucleotide	403-447 of Seq. Id. No. 159	166
		14 Amino Acid		167
	5	48 Nucleotide	419-466 of Seq. Id. No. 159	168
		15 Amino Acids		169
20	6	27 Nucleotide	454-480 of Seq. Id. No. 159	170
		8 Amino Acid		171
	7	39 Nucleotide	610-648 of Seq. Id. No. 159	172
		12 Amino Acid		173
	8	165 Nucleotide	658-822 of Seq. Id. No. 159	174
25		54 Amino Acid		175
	9	132 Nucleotide	691-822 of Seq. Id. No. 159	176
		43 Amino Acids		177
	10	123 Nucleotide	700-822 of Seq. Id. No. 159	178
		40 Amino Acid		179
30	11	111 Nucleotide	712-822 of Seq. Id. No. 159	180
		36 Amino Acid		181
	12	57 Nucleotide	945-1001 of Seq. Id. No. 159	182
		18 Amino Acid		183
35	13	18 Nucleotide	952-969 of Seq. Id. No. 159	184
		5 Amino Acids		185
	14	15 Nucleotide	962-976 of Seq. Id. No. 159	186
		4 Amino Acid		187
	15	99 Nucleotide	973-1071 of Seq. Id. No. 159	188
		32 Amino Acid		189
40	16	12 Nucleotide	1071-1082 of Seq. Id. No. 159	190
		3 Amino Acid		191
	17	63 Nucleotide	1131-1193 of Seq. Id. No. 159	192
		20 Amino Acid		193
	18	42 Nucleotide	1152-1193 of Seq. Id. No. 159	194
45		13 Amino Acids		195
	19	12 Nucleotide	1165-1176 of Seq. Id. No. 159	196
		3 Amino Acids		197

TABLE 7

OPEN READING FRAMES FOR CNI-00728

OPEN READING FRAME NUMBER	LENGTH	LOCATION	SEQUENCE ID. NO.
1	129 Nucleotide	30-158 of Seq. Id. No. 198	199
	42 Amino Acid		200
2	69 Nucleotide	70-138 of Seq. Id. No. 198	201
	22 Amino Acid		202
3	42 Nucleotide	117-158 of Seq. Id. No. 198	203
	13 Amino Acid		204
4	39 Nucleotide	187-225 of Seq. Id. No. 198	205
	12 Amino Acid		206
5	33 Nucleotide	193-225 of Seq. Id. No. 198	207
	10 Amino Acid		208
6	24 Nucleotide	202-225 of Seq. Id. No. 198	209
	7 Amino Acid		210
7	15 Nucleotide	225-239 of Seq. Id. No. 198	211
	4 Amino Acid		212
8	21 Nucleotide	331-351 of Seq. Id. No. 198	213
	6 Amino Acid		214
9	42 Nucleotide	384-425 of Seq. Id. No. 198	215
	13 Amino Acid		216
10	60 Nucleotide	404-463 of Seq. Id. No. 198	217
	19 Amino Acid		218
11	15 Nucleotide	536-550 of Seq. Id. No. 198	219
	4 Amino Acid		220
12	39 Nucleotide	626-664 of Seq. Id. No. 198	221
	12 Amino Acid		222
13	102 Nucleotide	689-790 of Seq. Id. No. 198	223
	33 Amino Acid		224
14	60 Nucleotide	731-790 of Seq. Id. No. 198	225
	19 Amino Acid		226
15	87 Nucleotide	738-824 of Seq. Id. No. 198	227
	28 Amino Acid		228
16	180 Nucleotide	910-1089 of Seq. Id. No. 198	229
	59 Amino Acid		230
17	99 Nucleotide	991-1089 of Seq. Id. No. 198	231
	32 Amino Acid		232
18	27 Nucleotide	1063-1089 of Seq. Id. No. 198	233
	8 Amino Acid		234

19	150 Nucleotide	1124-1273 of Seq. Id. No. 198	235
	49 Amino Acid		236
20	54 Nucleotide	1143-1196 of Seq. Id. No. 198	237
	17 Amino Acid		238
21	87 Nucleotide	1187-1273 of Seq. Id. No. 198	239
	28 Amino Acid		240
22	42 Nucleotide	1242-1283 of Seq. Id. No. 198	241
	13 Amino Acid		242
23	15 Nucleotide	1306-1320 of Seq. Id. No. 198	243
	4 Amino Acids		244
24	139 Nucleotide	1382-1466 of Seq. Id. No. 198	245
	46 Amino Acids		246

TABLE 8**OPEN READING FRAMES FOR CNI-00729**

OPEN READING FRAME NUMBER	LENGTH	LOCATION	SEQUENCE ID. NO.
1	1386 Nucleotide	140-1525 of Seq. Id. No. 247	248
	461 Amino Acid		249
2	75 Nucleotide	213-287 of Seq. Id. No. 247	250
	24 Amino Acid		251
3	69 Nucleotide	219-287 of Seq. Id. No. 247	252
	22 Amino Acid		253
4	39 Nucleotide	357-395 of Seq. Id. No. 247	254
	12 Amino Acid		255
5	72 Nucleotide	417-488 of Seq. Id. No. 247	256
	23 Amino Acid		257
6	1068 Nucleotide	458-1525 of Seq. Id. No. 247	258
	355 Amino Acid		259
7	12 Nucleotide	477-488 of Seq. Id. No. 247	260
	3 Amino Acid		261
8	1038 Nucleotide	488-1525 of Seq. Id. No. 247	262
	345 Amino Acid		263
9	918 Nucleotide	608-1525 of Seq. Id. No. 247	264
	305 Amino Acid		265
10	888 Nucleotide	638-1525 of Seq. Id. No. 247	266
	295 Amino Acid		267
11	75 Nucleotide	699-773 of Seq. Id. No. 247	268
	24 Amino Acid		269
12	663 Nucleotide	863-1525 of Seq. Id. No. 247	270
	220 Amino Acid		271
13	462 Nucleotide	1064-1525 of Seq. Id. No. 247	272
	153 Amino Acid		273
14	432 Nucleotide	1094-1525 of Seq. Id. No. 247	274
	143 Amino Acid		275
15	423 Nucleotide	1103-1525 of Seq. Id. No. 247	276
	140 Amino Acid		277
16	339 Nucleotide	1187-1525 of Seq. Id. No. 247	278
	112 Amino Acid		279
17	63 Nucleotide	1290-1352 of Seq. Id. No. 247	280
	20 Amino Acid		281
18	33 Nucleotide	1320-1352 of Seq. Id. No. 247	282
	10 Amino Acid		283
19	238 Nucleotide	1422-1659 of Seq. Id. No. 247	284
	79 Amino Acid		285

20	78 Nucleotide	1448-1525 of Seq. Id. No. 247	286
	25 Amino Acid		287
21	67 Nucleotide	1593-1659 of Seq. Id. No. 247	288
	22 Amino Acids		289
22	41 Nucleotide	1619-1659 of Seq. Id. No. 247	290
	13 Amino Acids		291

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TABLE 9**OPEN READING FRAMES FOR CNI-00730**

5	OPEN READING FRAME NUMBER	LENGTH	LOCATION	SEQUENCE ID. NO.
10	1	429 Nucleotide 142 Amino Acid	128-556 of Seq. Id. No. 292	293 294
	2	30 Nucleotide 9 Amino Acid	264-293 of Seq. Id. No. 292	295 296
	3	18 Nucleotide 5 Amino Acid	276-293 of Seq. Id. No. 292	297 298
15	4	21 Nucleotide 6 Amino Acid	435-455 of Seq. Id. No. 292	299 300
	5	51 Nucleotide 16 Amino Acids	474-524 of Seq. Id. No. 292	301 302
20	6	51 Nucleotide 16 Amino Acid	506-556 of Seq. Id. No. 292	303 304
	7	33 Nucleotide 10 Amino Acid	524-556 of Seq. Id. No. 292	305 306
	8	51 Nucleotide 16 Amino Acid	573-623 of Seq. Id. No. 292	307 308
25	9	74 Nucleotide 24 Amino Acids	649-722 of Seq. Id. No. 292	309 310

TABLE 10**OPEN READING FRAMES FOR CNI-00731**

5	OPEN READING FRAME NUMBER	LENGTH	LOCATION	SEQUENCE ID. NO.
10	1	48 Nucleotide	56-103 of Seq. Id. No. 311	312
		15 Amino Acid		313
	2	24 Nucleotide	80-103 of Seq. Id. No. 311	314
		7 Amino Acid		315
15	3	18 Nucleotide	86-103 of Seq. Id. No. 311	316
		5 Amino Acid		317
	4	99 Nucleotide	107-205 of Seq. Id. No. 311	318
		32 Amino Acid		319
	5	72 Nucleotide	199-270 of Seq. Id. No. 311	320
		23 Amino Acids		321
20	6	36 Nucleotide	235-270 of Seq. Id. No. 311	322
		11 Amino Acid		323
	7	98 Nucleotide	267-364 of Seq. Id. No. 311	324
		32 Amino Acids		325

TABLE 11**OPEN READING FRAMES FOR CNI-00732**

OPEN READING FRAME NUMBER	LENGTH	LOCATION	SEQUENCE ID. NO.
1	24 Nucleotide	23-46 of Seq. Id. No. 326	327
	7 Amino Acid		328
2	63 Nucleotide	100-162 of Seq. Id. No. 326	329
	20 Amino Acid		330
3	108 Nucleotide	418-525 of Seq. Id. No. 326	331
	35 Amino Acid		332
4	18 Nucleotide	611-628 of Seq. Id. No. 326	333
	5 Amino Acid		334
5	51 Nucleotide	671-721 of Seq. Id. No. 326	335
	16 Amino Acids		336
6	36 Nucleotide	686-721 of Seq. Id. No. 326	337
	11 Amino Acid		338
7	30 Nucleotide	727-756 of Seq. Id. No. 326	339
	9 Amino Acid		340
8	152 Nucleotide	895-1046 of Seq. Id. No. 326	341
	50 Amino Acids		342

Alternative or differential splicing of a gene that encodes any of the open reading frames shown in Figures 4-13 can also generate an alternative or differential protective sequence product. For example, a gene that generates one of the protective sequence products shown in Figures 4-13 may be encoded by 4 out of 6 exons that comprise the entire gene; alternative or differential splicing of the gene can generate other protective sequence products that are encoded by 1, 2, 3, 4, 5, or 6 of the exons in the gene (Lewin, 2000, Genes VII, Oxford University Press, 702-705). The present invention also includes nucleic acid molecules comprising nucleic acids that separately encode these alternative or differential protective sequence products.

In a specific embodiment, the nucleic acid molecules comprise nucleic acids that encode an open reading frame of at least 3 contiguous amino acid residues from a full-length protein. In alternate embodiments, the nucleic acid molecules comprise an open reading frame which encodes at least about 5, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, 350, 400, 450 or more contiguous amino acid residues of a protein.

The sequence obtained from clones containing partial coding sequences or non-coding sequences can be used to obtain the entire coding region by using the RACE method, for example (Chenchik, et al., 1995, CLONTECHniques (X) 1: 5-8; Barnes, 1994, Proc. Natl. Acad. Sci. USA 91: 2216-2220; and Cheng et al., Proc. Natl. Acad. Sci. USA 91: 5695-5699). Oligonucleotides can be designed based on the sequence obtained from the partial clone that can amplify a reverse transcribed mRNA encoding the entire coding sequence. Alternatively, probes can be used to screen cDNA libraries prepared from an appropriate cell or cell line in which the protective sequence is transcribed.

With respect to allelic variants of protective sequences associated with a condition, disorder, or disease involving cell death, any and all such nucleotide variations and resulting amino acid polymorphisms or variations which are the result of natural allelic variation of the protective sequence are intended to be within the scope of the present invention. Such allelic variants include, but are not limited to, ones that do not alter the functional activity of the protective sequence product.

With respect to the cloning of additional allelic variants of the isolated protective sequence and homologues and orthologs from other species (*e.g.*, guinea pig, cow, mouse), the isolated protective sequences disclosed herein may be labeled and used to screen

a cDNA library constructed from mRNA obtained from appropriate cells or tissues (*e.g.*, brain) derived from the organism (*e.g.*, guinea pig, cow and mouse) of interest. The hybridization conditions used generally should be of a lower stringency when the cDNA library is derived from an organism different from the type of organism from which the labeled sequence was derived, and can routinely be determined based on, *e.g.*, relative relatedness of the target and reference organisms.

Alternatively, the labeled fragment may be used to screen a genomic library derived from the organism of interest, again, using appropriately stringent conditions. Appropriate stringency conditions are well known to those of skill in the art as discussed above, and will vary predictably depending on the specific organisms from which the library and the labeled sequences are derived. For guidance regarding such conditions, *see*, for example, Sambrook, *et al.*, 1989, *Molecular Cloning, A Laboratory Manual*, Second Edition, Cold Spring Harbor Press, N.Y.; and Ausubel, *et al.*, 1989-1999, *Current Protocols in Molecular Biology*, Green Publishing Associates and Wiley Interscience, N.Y., both of which are incorporated herein by reference in their entirety.

Additionally, the cloning of homologs and orthologs of the isolated protective sequence from other species (*e.g.* mouse) could also occur using the knowledge of syntenic regions and/or genes. Syntenic genes are genes which are believed to be located on the same chromosome because they are lost along with a marker gene which is known to be located on that chromosome. There are well-established genetic maps of specific chromosome regions that show syntenic regions between chromosomes of humans and other species that can be utilized, by one skilled in the art, for this purpose.

Further, a protective sequence allelic variant may be isolated from, for example, human nucleic acid, by performing PCR using two degenerate oligonucleotide primer pools designed on the basis of amino acid sequences within the protective sequence product of interest. The template for the reaction may be cDNA obtained by reverse transcription of mRNA prepared from, for example, human or non-human cell lines or tissue known or suspected to express a wild type or mutant protective sequence allele. In one embodiment, the allelic variant is isolated from an individual who has a condition, disorder, or disease involving cell death. Such variants are described in the examples below.

The PCR product may be subcloned and sequenced to ensure that the amplified sequences represent the sequences of a protective nucleic acid sequence. The PCR fragment may then be used to isolate a full-length cDNA clone by a variety of methods. For example, the amplified fragment may be labeled and used to screen a bacteriophage cDNA library. Alternatively, the labeled fragment may be used to isolate genomic clones via the screening of a genomic library.

PCR technology also may be utilized to isolate full-length cDNA sequences. For example, RNA may be isolated, following standard procedures, from an appropriate cellular or tissue source. A reverse transcription reaction may be performed on the RNA using an oligonucleotide primer specific for the most 5' end of the amplified fragment for the priming of first strand synthesis. The resulting RNA/DNA hybrid may then be "tailed" with guanines using a standard terminal transferase reaction. The hybrid may be digested with RNAase H and second strand synthesis may then be primed with a poly-C primer. Thus, cDNA sequences upstream of the amplified fragment may easily be isolated. For a review of cloning strategies which may be used, see *e.g.*, Sambrook *et al.*, 1989, *supra*, or Ausubel *et al.*, *supra*.

In cases where the isolated protective sequence is the normal, or wild type gene, this gene may be used to isolate mutant alleles of the protective sequence. Such an isolation is preferable in processes and disorders that are known or suspected to have a genetic basis. Mutant alleles may be isolated from individuals either known or suspected to have a genotype which contributes to symptoms of conditions, disorders, or diseases involving cell death. Mutant alleles and mutant allele products may then be utilized in the therapeutic and diagnostic assay systems described below.

A cDNA of the mutant protective sequence may be isolated, for example, by using PCR, a technique well known to those of skill in the art. In this case, the first cDNA strand may be synthesized by hybridizing an oligo-dT oligonucleotide to mRNA isolated from tissue known or suspected to be expressed in an individual putatively carrying the mutant allele, and by extending the new strand with reverse transcriptase. The second strand of the cDNA is then synthesized using an oligonucleotide that hybridizes specifically to the 5' end of the normal protective sequence. Using these two primers, the product is then amplified via PCR, cloned into a suitable vector and subjected to DNA sequence analysis

through methods well known to those of skill in the art. By comparing the DNA sequence of the mutant protective sequence to that of the normal protective sequence, the mutation(s) responsible for the loss or alteration of function of the mutant gene product can be ascertained.

5 Alternatively, a genomic or cDNA library can be constructed and screened using DNA or RNA, respectively, from a tissue known to or suspected of expressing the protective sequence of interest in an individual suspected of or known to carry the mutant allele. The normal protective sequence or any suitable fragment thereof may then be labeled and used as a probe to identify the corresponding mutant allele in the library. The clone
10 containing this protective sequence may then be purified through methods routinely practiced in the art, and subjected to sequence analysis as described above in this Section.

 Additionally, an expression library can be constructed utilizing DNA isolated from or cDNA synthesized from a tissue known to or suspected of expressing the protective sequence of interest in an individual suspected of or known to carry the mutant allele. In this
15 manner, protective sequence products made by the tissue containing the putative mutant alleles may be expressed and screened using standard antibody screening techniques in conjunction with antibodies raised against the normal protective sequence product, as described, below, in Section 5.3 (For screening techniques, see, for example, Harlow, E. and Lane, eds., 1988, "Antibodies: A Laboratory Manual", Cold Spring Harbor Press, Cold Spring
20 Harbor.) In cases where the mutation results in an expressed protective sequence product with altered function (*e.g.*, as a result of a missense mutation), a polyclonal set of antibodies are likely to cross-react with the mutant protective sequence product. Library clones detected via their reaction with such labeled antibodies can be purified and subjected to sequence analysis as described in this Section, above.

25 The invention also includes nucleic acid molecules, preferably DNA molecules that are the complements of the nucleic acids of the preceding paragraphs.

 In certain embodiments, the protective nucleic acid molecules of the invention are present as part of protective nucleic acid molecules comprising nucleic acid sequences which do not contain heterologous (*e.g.*, cloning vector or expression vector) sequences. In
30 other embodiments, the protective nucleic acid molecules of the invention further comprise vector sequences, *e.g.*, cloning vectors or expression vectors.

5.2 Protein Products of the Protective Sequences

Protective sequence products or fragments thereof of the invention can be prepared for a variety of uses, including but not limited to, prophylactic or therapeutic modulators of protective sequence product function, for the generation of antibodies, diagnostic assays, or for the identification of other cellular or extracellular protective sequence products involved in the regulation of conditions, disorders, or diseases involving cell death.

The protective sequence products of the invention include, but are not limited to, human protective sequence products and non-human protective sequence products, *e.g.*, mammalian (such as bovine or guinea pig), protective sequence products.

Protective sequence products of the invention, sometimes referred to herein as a "protective sequence protein" or "protective sequence polypeptide," includes those gene products encoded by any of up to six translational reading frames of the protective sequence sequences depicted in Table 1, as well as gene products encoded by other human allelic variants and non-human variants of protective sequence products which can be identified by the methods herein described. Among such protective sequence product variants are protective sequence products comprising amino acid residues encoded by polymorphisms of such protective sequence products.

In addition, protective sequence products of the invention may include proteins that represent functionally equivalent gene products. Functionally equivalent protective sequence products may include, for example, protective sequence products encoded by one of the nucleic acid molecules described in Section 5.1, above. In preferred embodiments, such functionally equivalent protective sequence products are naturally occurring gene products. Functionally equivalent protective sequence products also include gene products which retain at least one of the biological activities of the protective sequence products described above, and/or which are recognized by and bind to antibodies (polyclonal or monoclonal) directed against protective sequence products of the invention.

Equivalent protective sequence products may contain deletions, including internal deletions, additions, including additions yielding fusion proteins, or substitutions of amino acid residues within and/or adjacent to the amino acid sequence encoded by the protective sequence sequences described, above, in Section 5.1. Generally, deletions will be

deletions of single amino acid residues, or deletions of no more than about 2, 3, 4, 5, 10 or 20 amino acid residues, either contiguous or non-contiguous. Generally, additions or substitutions, other than additions which yield fusion proteins, will be additions or substitutions of single amino acid residues, or additions or substitutions of no more than about 2, 3, 4, 5, 10 or 20 amino acid residues, either contiguous or non-contiguous. Preferably, these modifications result in a "silent" change, in that the change produces a protective sequence product with the same activity as the original protective sequence product. However, nucleic acid changes resulting in amino acid additions or substitutions may also be made for the purpose of modifying the protective sequence product in order to generally enhance their use as therapeutic agents or components for assays, such modifications to include, but not be limited to, stabilizing the product against degradation, enhancing pharmacokinetic properties, modifying site tropisms at the level of cells, tissues, organs, or organisms.

Amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues involved. For example, nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan and methionine; polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine and glutamine; positively charged (basic) amino acids include arginine, lysine and histidine; and negatively charged (acidic) amino acids include aspartic acid and glutamic acid. Additionally, non-natural amino acids, including, but not limited to, D-amino acids may be used.

Alternatively, where alteration of function is desired, addition(s), deletion(s) or non-conservative alterations can produce altered, including reduced-activity, protective sequence products. Such alterations can, for example, alter one or more of the biological functions of the protective sequence product. Further, such alterations can be selected so as to generate protective sequence products which include, but are not limited to, products which are better suited for expression, scale up, *etc.* in the host cells chosen. For example, cysteine residues can be deleted or substituted with another amino acid residue in order to eliminate disulfide bridges.

Protective sequence products of the invention also include gene products generated by alternative or differential splicing patterns of a gene that encodes for the

peptides shown in Figures 4-13. An isolated gene often includes alternating exons and introns; as a result, the same gene can generate a variety of gene products by alternative or differential forms of splicing.

Protein fragments and/or peptides of the invention may comprise at least as many contiguous amino acid residues as necessary to represent an epitope fragment (that is to be recognized by an antibody directed to the protein). Examples of such protein fragments and/or peptides of the invention are shown by the open reading frames of the protective sequences shown in Figures 4-13, and described in Tables 2-11, respectively. In one nonlimiting embodiment of the invention, such protein fragments or peptides comprise at least about 3 contiguous amino acid residues from a full-length protein. In alternate embodiments, the protein fragments and peptides of the invention can comprise about 5, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, 350, 400, 450 or more contiguous amino acid residues of a protein.

Peptides and/or proteins corresponding to one or more domains of the protein as well as fusion proteins in which a protein, or a portion of a protein such as a truncated protein or peptide or a protein domain, is fused to an unrelated protein are also within the scope of this invention. Such proteins and peptides can be designed on the basis of the nucleic acids disclosed in Section 5.1, above. Fusion proteins include, but are not limited to, IgFc fusions which stabilize the protein or peptide and prolong half-life *in vivo*; or fusions to any amino acid sequence which allows the fusion protein to be anchored to the cell membrane; or fusions to an enzyme, fluorescent protein, luminescent protein or a epitope tagged protein or peptide which provides a marker function.

The protein sequences described above can include a domain, which comprises a protein transduction domain which targets the protective sequence product for delivery to various tissues and more particularly across the brain blood barrier, using, for example, the protein transduction domain of human immunodeficiency virus TAT protein (Schwarze *et al.*, 1999, Science 285: 1569-72).

The protein sequences described above can include a domain, which comprises a signal sequence that targets the gene product for secretion. As used herein, a signal sequence includes a peptide of at least about 15 or 20 amino acid residues in length which occurs at the N-terminus of secretory and membrane-bound proteins and which

contains at least about 70% hydrophobic amino acid residues such as alanine, leucine, isoleucine, phenylalanine, proline, tyrosine, tryptophan or valine. In a preferred embodiment, a signal sequence contains at least about 10 to 40 amino acid residues, preferably about 19-34 amino acid residues and has at least about 60-80%, more preferably 65-75% and more preferably at least about 70% hydrophobic residues. A signal sequence serves to direct a protein containing such a sequence to a lipid bilayer.

A signal sequence of a polypeptide of the invention can be used to facilitate secretion and isolation of the secreted protein or other proteins of interest. Signal sequences are typically characterized by a core of hydrophobic amino acids, which are generally cleaved from the mature protein during secretion in one or more cleavage events. Such signal peptides contain processing sites that allow cleavage of the signal sequence from the mature proteins as they pass through the secretory pathway. Thus, the invention pertains to the described polypeptides having a signal sequence (that is, "immature" polypeptides), as well as to the signal sequences themselves and to the polypeptides in the absence of a signal sequence (*i.e.*, the "mature" cleavage products). It is to be understood that polypeptides of the invention can further comprise polypeptides comprising any signal sequence having characteristics as described above and a mature polypeptide sequence.

In one embodiment, a nucleic acid sequence encoding a signal sequence of the invention can be operably linked in an expression vector to a protein of interest, such as a protein which is ordinarily not secreted or is otherwise difficult to isolate. The signal sequence directs secretion of the protein, such as from a eukaryotic host into which the expression vector is transformed, and the signal sequence is subsequently or concurrently cleaved. The protein can then be readily purified from the extracellular medium by art recognized methods. Alternatively, the signal sequence can be linked to the protein of interest using a sequence which facilitates purification, such as with a GST domain.

Finally, the proteins of the invention also include protein sequences wherein domains encoded by any transcriptional or post-transcriptional, and/or translational or post-translational modifications, or fragments thereof, have been deleted. The polypeptides of the invention can further comprise posttranslational modifications, including, but not limited to glycosylations, acetylations and myrisalations.

The protective sequence products, peptide fragments thereof and fusion proteins thereof may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing the protective sequence products, polypeptides, peptides, fusion peptide and fusion polypeptides of the invention by expressing nucleic acid containing protective sequence sequences are described herein. Methods that are well known to those skilled in the art can be used to construct expression vectors containing protective sequence product coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, *in vitro* recombinant DNA techniques, synthetic techniques and *in vivo* genetic recombination. See, for example, the techniques described in Sambrook, *et al.*, 1989, *supra*, and Ausubel, *et al.*, 1989, *supra*. Alternatively, RNA capable of encoding protective sequence product sequences may be chemically synthesized using, for example, synthesizers. See, for example, the techniques described in "Oligonucleotide Synthesis", 1984, Gait, ed., IRL Press, Oxford.

A variety of host-expression vector systems may be utilized to express the protective sequence product coding sequences of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, exhibit the protective sequence product of the invention *in situ*. These include, but are not limited to, microorganisms such as bacteria (*e.g.*, *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing protective sequence product coding sequences; yeast (*e.g.*, *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing the protective sequence product coding sequences; insect cell systems infected with recombinant virus expression vectors (*e.g.*, baculovirus) containing the protective sequence product coding sequences; plant cell systems infected with recombinant virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (*e.g.*, Ti plasmid) containing protective sequence product coding sequences; or mammalian cell systems (*e.g.*, COS, CHO, BHK, 293, 3T3) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (*e.g.*, metallothioneine promoter) or from mammalian viruses (*e.g.*, the adenovirus late promoter; the vaccinia virus 7.5K promoter).

In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the protective sequence product being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of protective sequence product or for raising
5 antibodies to protective sequence product, for example, vectors which direct the expression of high levels of fusion protein products which are readily purified may be desirable. Such vectors include, but are not limited to, the *E. coli* expression vector pUR278 (Ruther *et al.*, 1983, EMBO J. 2:1791), in which the protective sequence product coding sequence may be ligated individually into the vector in frame with the *lacZ* coding region so that a fusion
10 protein is produced; pIN vectors (Inouye and Inouye, 1985, Nucleic Acids Res. 13:3101-3109; Van Heeke and Schuster, 1989, J. Biol. Chem. 264:5503-5509); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the
15 presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned protective sequence product can be released from the GST moiety.

In an insect system, *Autographa californica*, nuclear polyhidrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera
20 frugiperda* cells. The protective sequence product coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter). Successful insertion of protective sequence product coding sequence will result in inactivation of the polyhedrin gene and production of non-occluded recombinant virus (*i.e.*,
25 virus lacking the proteinaceous coat coded for by the polyhedrin gene). These recombinant viruses are then used to infect *Spodoptera frugiperda* cells in which the inserted gene is expressed. (*e.g.*, see Smith, *et al.*, 1983, J. Virol. 46:584; Smith, U.S. Patent No. 4,215,051).

In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the protective
30 sequence product coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, *e.g.*, the late promoter and tripartite leader

sequence. This chimeric gene may then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non-essential region of the viral genome (*e.g.*, region E1 or E3) will result in a recombinant virus that is viable and capable of expressing protective sequence products in infected hosts. (*See, e.g.*, Logan and Shenk, 1984, *Proc. Natl. Acad. Sci. USA* 81:3655-3659). Specific initiation signals may also be required for efficient translation of inserted protective sequence product coding sequences. These signals include the ATG initiation codon and adjacent sequences. In cases where an entire protective sequence, including its own initiation codon and adjacent sequences, is inserted into the appropriate expression vector, no additional translational control signals may be needed. However, in cases where only a portion of the protective sequence coding sequence is inserted, exogenous translational control signals, including, perhaps, the ATG initiation codon, must be provided. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, *etc.* (*see* Bittner, *et al.*, 1987, *Methods in Enzymol.* 153:516-544).

In addition, a host cell strain may be chosen that modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (*e.g.*, glycosylation) and processing (*e.g.*, cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells that possess the cellular machinery for proper processing of the primary transcript, glycosylation and phosphorylation of the gene product may be used. Such mammalian host cells include, but are not limited to, CHO, VERO, BHK, HeLa, COS, MDCK, 293, 3T3 and WI38. Additional host cells derived from neuronal tissue include, but are not limited to, PC-12 cells and primary dissociated neurons which are removed from the brain and grown in culture.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines that stably express the protective sequence product may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (*e.g.*, promoter, enhancer, sequences, transcription terminators, polyadenylation sites, *etc.*), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines that express the protective sequence product. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that affect the endogenous activity of the protective sequence product.

A number of selection systems may be used, including, but not limited to, the herpes simplex virus thymidine kinase (Wigler, *et al.*, 1977, *Cell* 11:223), hypoxanthine-guanine phosphoribosyltransferase (Szybalska and Szybalski, 1962, *Proc. Natl. Acad. Sci. USA* 48:2026), and adenine phosphoribosyltransferase (Lowy, *et al.*, 1980, *Cell* 22:817) genes can be employed in tk⁻, hgp^rt⁻ or ap^rt⁻ cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler, *et al.*, 1980, *Proc. Natl. Acad. Sci. USA* 77:3567; O'Hare, *et al.*, 1981, *Proc. Natl. Acad. Sci. USA* 78:1527); gpt, which confers resistance to mycophenolic acid (Mulligan and Berg, 1981, *Proc. Natl. Acad. Sci. USA* 78:2072); neo, which confers resistance to the aminoglycoside G-418 (Colberre-Garapin, *et al.*, 1981, *J. Mol. Biol.* 150:1); and hyg^r, which confers resistance to hygromycin (Santerre, *et al.*, 1984, *Gene* 30:147).

Alternatively, the expression characteristics of an endogenous protective sequence within a cell line or microorganism may be modified by inserting a heterologous DNA regulatory element into the genome of a stable cell line or cloned microorganism such that the inserted regulatory element is operatively linked with the endogenous protective sequence. For example, an endogenous protective sequence which is normally "transcriptionally silent", *i.e.*, a protective sequence which is normally not expressed, or is

expressed only at very low levels in a cell line or microorganism, may be activated by inserting a regulatory element which is capable of promoting the expression of a normally expressed protective sequence product in that cell line or microorganism. Alternatively, a transcriptionally silent, endogenous protective sequence may be activated by insertion of a promiscuous regulatory element which works across cell types.

Methods, which are well known to those skilled in the art, can be used to construct vectors containing the protective sequence operatively associated with appropriate transcriptional/translational control signals. These methods include *in vitro* recombinant DNA techniques, and synthetic techniques. See, for example, the techniques described in Sambrook, *et al.*, 1992, Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, N.Y. and Ausubel *et al.*, 1989, Current Protocols in Molecular Biology, Greene Publishing Associates & Wiley Interscience, N.Y.

The protective sequences may be associated operatively with a variety of different promoter/enhancer elements. The expression elements of these vectors may vary in their strength and specificities. Depending on the host/vector system utilized, any one of a number of suitable transcription and translation elements may be used. The promoter may be in the form of the promoter that is associated naturally with the gene of interest.

Alternatively, the DNA may be positioned under the control of a recombinant or heterologous promoter, *i.e.*, a promoter that is not associated normally with that gene. For example, tissue specific promoter/enhancer elements may be used to regulate the expression of the transferred DNA in specific cell types. Examples of transcriptional control regions which exhibit tissue specificity which have been described and could be used, include, but are not limited to: choline acetyltransferase (ChAT) gene control region which is active in cholinergic cells in the brain (Lonnerberg *et al.*, 1996, JBC 271:33358-65; Lonnerberg *et al.*, 1995, PNAS 92: 4046-50; Ibenez and Perrson, 1991 Eur. J. Neurosci. 3: 1309-15), mouse Thy-1.2 gene control region which is active in adult neurons including hippocampus, thalamus, cerebellum, cortex, RGC, DRG, and MN in the brain (Caroni, 1997, J Neurosci. Meth. 71: 3-9; Vidal *et al.*, 1990, EMBO J 9: 833-40), neuron specific enolase (NSE) gene control region which is active in pan-neuronal, neuron specific, deep layers of cerebral and neocortex (not in white matter) areas of the brain (Hannas-Djebbara *et al.*, 1997, Brain Res. Mol. Brain Res. 46: 91-9; Peel *et al.*, 1997, Gene Therapy 4: 16-24; Twyman *et al.*, 1997, J Mol Neurosci 8: 63-73;

Forss-Petter *et al.*, 1990, *Neuron* 5:187-97), elastase I gene control region which is active in pancreatic acinar cells (Swift *et al.*, 1984, *Cell* 38:639-646; Ornitz *et al.*, 1986, Cold Spring Harbor Symp. Quant. Biol. 50:399-409; MacDonald, 1987, *Hepatology* 7:42S-51S); insulin gene control region which is active in pancreatic beta cells (Hanahan, 1985, *Nature* 315:115-122); immunoglobulin gene control region which is active in lymphoid cells (Grosschedl *et al.*, 1984, *Cell* 38:647-658; Adams *et al.*, 1985, *Nature* 318:533-538; Alexander *et al.*, 1987, *Mol. Cell. Biol.* 7:1436-1444); albumin gene control region which is active in liver (Pinkert *et al.*, 1987, *Genes and Devel.* 1:268-276); alpha-fetoprotein gene control region which is active in liver (Krumlauf *et al.*, 1985, *Mol. Cell. Biol.* 5:1639-1648; Hammer *et al.*, 1987, *Science* 235:53-58); alpha-1-antitrypsin gene control region which is active in liver (Kelsey *et al.*, 1987, *Genes and Devel.* 1:161-171); beta-globin gene control region which is active in myeloid cells (Magram *et al.*, 1985, *Nature* 315:338-340; Kollias *et al.*, 1986, *Cell* 46:89-94); myelin basic protein gene control region which is active in oligodendrocyte cells in the brain (Readhead *et al.*, 1987, *Cell* 48:703-712); myosin light chain-2 gene control region which is active in skeletal muscle (Shani, 1985, *Nature* 314:283-286) and gonadotropic releasing hormone gene control region which is active in the hypothalamus (Mason *et al.*, 1986, *Science* 234:1372-1378). Promoters isolated from the genome of viruses which grow in mammalian cells (*e.g.*, CMV, RSV, vaccinia virus 7.5K, SV40, HSV, adenoviruses MLP, and MMTV LTR promoters) may be used, as well as promoters produced by recombinant DNA or synthetic techniques. Further, promoters specifically activated within bone, *i.e.*, the osteocalcin promoter, which is specifically activated within cells of osteoblastic lineage, may be used to target expression of nucleic acids within bone cells.

A heterologous regulatory element may be inserted into a stable cell line or cloned microorganism, such that it is operatively linked with an endogenous protective sequence, using techniques, such as targeted homologous recombination, which are well known to those of skill in the art, and described *e.g.*, in Chappel, U.S. Patent No. 5,272,071; PCT publication No. WO 91/06667, published May 16, 1991.

Alternatively, utilizing an antibody specific for the fusion protein being expressed may readily purify any fusion protein. For example, a system described by Janknecht, *et al.* allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht, *et al.*, 1991, *Proc. Natl. Acad. Sci. USA* 88:8972-8976). In

this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the gene's open reading frame is translationally fused to an amino-terminal tag consisting of six histidine residues. Extracts from cells infected with recombinant vaccinia virus are loaded onto Ni²⁺-nitriloacetic acid-agarose columns and histidine-tagged proteins are selectively eluted with imidazole-containing buffers.

The protective sequence products can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, *e.g.*, baboons, monkeys and chimpanzees may be used to generate transgenic animals. The term "transgenic," as used herein, refers to animals expressing protective sequences from a different species (*e.g.*, mice expressing human protective sequences), as well as animals which have been genetically engineered to overexpress endogenous (*i.e.*, same species) sequences or animals which have been genetically engineered to no longer express endogenous protective sequences (*i.e.*, "knock-out" animals), and their progeny.

Any technique known in the art may be used to introduce a protective sequence transgene into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Hoppe and Wagner, 1989, U.S. Pat. No. 4,873,191); retrovirus mediated gene transfer into germ lines (Van der Putten, *et al.*, 1985, *Proc. Natl. Acad. Sci., USA* 82:6148-6152); gene targeting in embryonic stem cells (Thompson, *et al.*, 1989, *Cell* 56:313-321); electroporation of embryos (Lo, 1983, *Mol. Cell. Biol.* 3:1803-1814); and sperm-mediated gene transfer (Lavitrano *et al.*, 1989, *Cell* 57:717-723) (For a review of such techniques, see Gordon, 1989, *Transgenic Animals*, *Intl. Rev. Cytol.* 115, 171-229).

Any technique known in the art may be used to produce transgenic animal clones containing a protective sequence transgene, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal or adult cells induced to quiescence (Campbell, *et al.*, 1996, *Nature* 380:64-66; Wilmut, *et al.*, *Nature* 385:810-813).

The present invention provides for transgenic animals which carry a protective sequence transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells, *i.e.*, mosaic animals. The transgene may be integrated as a single transgene or in concatamers, *e.g.*, head-to-head tandems or head-to-tail tandems. The transgene also

may be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko *et al.* (Lasko, *et al.*, 1992, *Proc. Natl. Acad. Sci. USA* 89:6232-6236). The regulatory sequences required for such a cell-type specific activation will depend on the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the cerebral transgene be integrated into the chromosomal site of the endogenous protective sequence, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleic acids homologous to the endogenous protective sequence are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleic acid of the endogenous protective sequence. The transgene also may be selectively introduced into a particular cell type, thus inactivating the endogenous protective sequence in only that cell type, by following, for example, the teaching of Gu, *et al.* (Gu, *et al.*, 1994, *Science* 265, 103-106). The regulatory sequences required for such a cell-type specific inactivation will depend on the particular cell type of interest, and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the recombinant protective sequence may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to assay whether integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis and RT-PCR (reverse transcriptase PCR). Samples of protective sequence-expressing tissue also may be evaluated immunocytochemically using antibodies specific for the transgene product.

Protective proteins can be used, *e.g.*, to treat cell death-related conditions, disorders, or diseases. Such protective sequence products include, but are not limited to, soluble derivatives such as peptides or polypeptides corresponding to one or more domains of the protective sequence product which are modified such that they are deleted for one or more hydrophobic domains. Alternatively, antibodies to the protein or anti-idiotypic antibodies which mimic the protective sequence product (including Fab fragments), modulators, antagonists or agonists can be used to treat cell death-related conditions, disorders, or

diseases involving the protective sequence product. In yet another approach, nucleotide constructs encoding such protective sequence products can be used to genetically engineer host cells to express such protective sequence products *in vivo*; these genetically engineered cells can function as "bioreactors" in the body delivering a continuous supply of protective sequence product, peptides and soluble polypeptides.

5.3 Antibodies to the Protective Sequence Products

Described herein are methods for the production of antibodies capable of specifically recognizing one or more protective sequence product epitopes or epitopes of conserved variants or peptide fragments of the protective sequence products of the invention. Further, antibodies that specifically recognize mutant forms of the protective sequence products of the invention are encompassed by the invention. The terms "specifically bind" and "specifically recognize" refer to antibodies which bind to protective sequence product epitopes involved in conditions, disorders, or diseases involving cell death at a higher affinity than they bind to protective sequence product epitopes not involved in such conditions, disorders, or diseases (*e.g.*, random epitopes).

Such antibodies may include, but are not limited to, polyclonal antibodies, monoclonal antibodies (mAbs), human, humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab')₂ fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies and epitope-binding fragments of any of the above. Such antibodies may be used, for example, in the detection of a protective sequence product in a biological sample and may, therefore, be utilized as part of a diagnostic or prognostic technique whereby patients may be tested for abnormal levels of protective sequence products, and/or for the presence of abnormal forms of such protective sequence products. Such antibodies also may be utilized in conjunction with, for example, compound screening schemes, as described, below, in Section 5.4.2, for the evaluation of the effect of test compounds on protective sequence product levels and/or activity. Additionally, such antibodies can be used in conjunction with the gene therapy techniques described below, in Section 5.4.1.3., to evaluate, for example, the normal and/or engineered cells prior to their introduction into the patient.

Antibodies derived from the protective sequence or protective sequence product, including, but not limited to, antibodies and anti-idiotypic antibodies that mimic activity or function additionally may be used in methods for inhibiting abnormal protective sequence product activity. Thus, such antibodies may, therefore, be utilized as part of treatment methods for protective sequence product-mediated conditions, disorders, or diseases.

For the production of antibodies against a protective sequence, various host animals may be immunized with a protective sequence or protective sequence product, or a portion thereof. Such host animals may include, but are not limited to, rabbits, mice and rats, to name but a few. Various adjuvants may be used to increase the immunological response, depending on the host species, including, but not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanin, dinitrophenol and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and *Corynebacterium parvum*.

Polyclonal antibodies are heterogeneous populations of antibody molecules derived from the sera of animals immunized with an antigen, such as protective sequence product, or an antigenic functional derivative thereof. For the production of polyclonal antibodies, host animals such as those described above, may be immunized with protective sequence product supplemented with adjuvants as also described above.

Monoclonal antibodies, which are homogeneous populations of antibodies to a particular antigen, may be obtained by any technique that provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique of Kohler and Milstein, (1975, *Nature* 256:495-497; and U.S. Patent No. 4,376,110), the human B-cell hybridoma technique (Kosbor *et al.*, 1983, *Immunology Today* 4:72; Cole *et al.*, 1983, *Proc. Natl. Acad. Sci. USA* 80:2026-2030), and the EBV-hybridoma technique (Cole *et al.*, 1985, *Monoclonal Antibodies And Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96). Such antibodies may be of any immunoglobulin class including IgG, IgM, IgE, IgA, IgD and any subclass thereof. The hybridoma producing the mAb of this invention may be cultivated *in vitro* or *in vivo*. Production of high titers of mAbs *in vivo* makes this the presently preferred method of production.

Additionally, recombinant antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the invention. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region. (See, *e.g.*, Cabilly et al., U.S. Patent No. 4,816,567; and Boss et al., U.S. Patent No. 4,816,397, which are incorporated herein by reference in their entirety.) Humanized antibodies are antibody molecules from non-human species having one or more complementarily determining regions (CDRs) from the non-human species and a framework region from a human immunoglobulin molecule. (See, *e.g.*, Queen, U.S. Patent No. 5,585,089, which is incorporated herein by reference in its entirety.) Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in PCT Publication No. WO 87/02671; European Patent Application 184,187; European Patent Application 171,496; European Patent Application 173,494; PCT Publication No. WO 86/01533; U.S. Patent No. 4,816,567; European Patent Application 125,023; Better et al. (1988) *Science* 240:1041-1043; Liu et al. (1987) *Proc. Natl. Acad. Sci. USA* 84:3439-3443; Liu et al. (1987) *J. Immunol.* 139:3521-3526; Sun et al. (1987) *Proc. Natl. Acad. Sci. USA* 84:214-218; Nishimura et al. (1987) *Canc. Res.* 47:999-1005; Wood et al. (1985) *Nature* 314:446-449; and Shaw et al. (1988) *J. Natl. Cancer Inst.* 80:1553-1559; Morrison (1985) *Science* 229:1202-1207; Oi et al. (1986) *Bio/Techniques* 4:214; U.S. Patent 5,225,539; Jones et al. (1986) *Nature* 321:552-525; Verhoeven et al. (1988) *Science* 239:1534; and Beidler et al. (1988) *J. Immunol.* 141:4053-4060.

Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Such antibodies can be produced, for example, using transgenic mice which are incapable of expressing endogenous immunoglobulin heavy and light chains genes, but which can express human heavy and light chain genes. The transgenic mice are immunized in the normal fashion with a selected antigen, *e.g.*, all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently

undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar (1995, *Int. Rev. Immunol.* 13:65-93). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., U.S. Patent 5,625,126; U.S. Patent 5,633,425; U.S. Patent 5,569,825; U.S. Patent 5,661,016; and U.S. Patent 5,545,806. In addition, companies such as Abgenix, Inc. (Fremont, CA), can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al. (1994) *Bio/technology* 12:899-903).

In addition, techniques developed for the production of "chimeric antibodies" (Morrison, et al., 1984, *Proc. Natl. Acad. Sci.*, 81:6851-6855; Neuberger, et al., 1984, *Nature* 312:604-608; Takeda, et al., 1985, *Nature*, 314:452-454) by splicing the genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region. (See, e.g., Cabilly et al., U.S. Patent No. 4,816,567; and Boss et al., U.S. Patent No. 4,816,397, which are incorporated herein by reference in their entirety.)

In addition, techniques have been developed for the production of humanized antibodies. (See, e.g., Queen, U.S. Patent No. 5,585,089, which is incorporated herein by reference in its entirety.) An immunoglobulin light or heavy chain variable region consists of a "framework" region interrupted by three hypervariable regions, referred to as complementarily determining regions (CDRs). The extent of the framework region and CDRs have been precisely defined (see, "Sequences of Proteins of Immunological Interest", Kabat, E. et al., U.S. Department of Health and Human Services (1983)). Briefly, humanized antibodies are antibody molecules from non-human species having one or more

CDRs from the non-human species and a framework region from a human immunoglobulin molecule.

Alternatively, techniques described for the production of single chain antibodies (U.S. Patent 4,946,778; Bird, 1988, *Science* 242:423-426; Huston, *et al.*, 1988, *Proc. Natl. Acad. Sci. USA* 85:5879-5883; and Ward, *et al.*, 1989, *Nature* 334:544-546) can be adapted to produce single chain antibodies against protective sequence products. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide.

Antibody fragments that recognize specific epitopes may be generated by known techniques. For example, such fragments include, but are not limited to: the F(ab')₂ fragments, which can be produced by pepsin digestion of the antibody molecule and the Fab fragments, which can be generated by reducing the disulfide bridges of the F(ab')₂ fragments. Alternatively, Fab expression libraries may be constructed (Huse, *et al.*, 1989, *Science* 246:1275-1281) to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity.

5.4 Uses of the Protective Sequences, Protective Sequence Products and Antibodies

Described herein are various uses and applications of protective sequences, protective sequence products, including peptide fragments and fusion proteins thereof and of antibodies and anti-idiotypic antibodies derived from the protective sequence products and peptide fragments thereof. The application relates to compositions and methods for the treatment of conditions, disorders, or diseases involving cell death. Such applications include, but are not limited to, the prophylactic or therapeutic use of protective sequences which, when introduced into a cell predisposed to undergo cell death or in the process of dying, to prevent, delay, or rescue a cell, cells, tissue, organs, or organisms from dying, as described below in Section 5.4.1

Additionally, such applications include methods for the treatment of conditions, disorders, or diseases involving cell death, including, but not limited to, those associated with the central nervous system including neurological and psychiatric conditions, disorders, or diseases, and others as described below, in Section 5.4.1.1, and for the

identification of compounds which modulate the expression of the protective sequence and/or the synthesis or activity of the protective sequence product, as described below, in Section 5.4.1. Such compounds can include, for example, other cellular products that are involved in such processes as the regulation of cell death. These compounds can be used, for example, in the amelioration of conditions, disorders, or diseases involving cell death.

One example of the type of injury that can cause cell death in neuronal cells is stroke, which often is the result of ischemic injury. A relatively broad time window (8 hours to perhaps several days or longer) exists between the onset of ischemic injury (*i.e.* cessation or marked reduction in blood flow) before most neural cells actually die. There are many complex pathways and perhaps hundreds of different signaling molecules which are likely to be involved, leaving many different intervention points each with the potential to prevent, delay, arrest and reverse the cell death program. These delayed biochemical intervention points represent ideal clinical intervention points as they correspond to the time period during which most stroke patients present for medical treatment.

Many current medications for the treatment of stroke affect the physical and biochemical events that are acutely related to the initial onset of stroke, and, thus, must be administered soon after the biochemical cascades begin. These approaches all suffer from the necessity of administering the drugs within a very brief time window following a stroke. However, many stroke patients do not even realize that they have suffered from a stroke until a time point at which many of the current treatments are ineffective. This is because many stroke patients often do not present at the emergency room prior to the passing of at least 13 hours from the onset of the stroke. The methods and compounds of the present invention, however, can be administered during the broader time window between stroke and the onset of the pathways leading to cell death.

In addition to stroke, a variety of other conditions, disorders, and diseases lead to the activation of the same biochemical cascades which lead to neuronal cell death in stroke. There is growing evidence that numerous other disease states that induce cell death programs are related to those induced by stroke. Cell death programs have been increasingly implicated in Alzheimer's disease, a well-known neurodegenerative condition which leads to substantial loss of specific neuronal populations in the neocortex and hippocampus. Vascular dementia (multi-infarct dementia) is another disorder in which stroke-like cell death pathways

are active. In vascular dementia, a repetitive process of small blood vessel diseases induces regional brain cell death, leading to a progressive loss of cognitive abilities. A partial list of other brain diseases which activate brain cell death pathways similar to those observed in stroke include, but are not limited to, Parkinson's disease, traumatic injury, Down's syndrome, Huntington's disease, HIV infection and intracranial infections.

One notable example from the preceding list is physical trauma to the nervous system. Although such trauma can be caused by a multitude of different physical insults to the head, neck, spine and other parts of the nervous system, all result in focal damage to, and death of, neural tissue and its component cells. Focally damaged areas behave similarly to stroke-induced infarcts in that a wider area of neural damage and death, a penumbra, is induced via biochemical and cellular mechanisms which are similar or identical to those occurring in stroke.

While, for clarity, the uses described in this section are primarily uses related to conditions, disorders, or diseases involving cell death, it is to be noted that each of the diagnostic and therapeutic treatments described herein can be additionally utilized in connection with other defects associated with the protective sequences of the invention.

Additionally, described herein are various applications of protective sequences, protective sequence products, genes, gene products, and/or their regulatory elements, including, but not limited to, prognostic and diagnostic evaluation of conditions, disorders, or diseases as described below in Section 5.4.1.1.

A variety of methods can be employed for the diagnostic and prognostic evaluation of conditions, disorders, or diseases involving cell death and for the identification of subjects having a predisposition to such conditions, disorders, or diseases.

Since protective sequences or protective sequence products need not normally be involved in all conditions, disorders, or diseases involving cell death, methods of the invention include, for example, modulating the expression of the protective sequence and/or the activity of the protective sequence product for the treatment of conditions, disorders, or diseases involving cell death which are normally mediated by some other gene.

For cell death related conditions, disorders, or diseases in which the protective sequences or protective sequence products are involved normally, such diagnostic and prognostic methods may, for example, utilize reagents such as the protective nucleic acids

described in Section 5.1, and antibodies directed against protective sequence products, including peptide fragments thereof, as described, above, in Section 5.3.

Specifically, such reagents may be used, for example, for:

5 (1) the detection of the presence of protective sequence mutations, or the detection of either over- or under-expression of the protective sequence relative to wild-type levels of expression;

(2) the detection of over- or under-abundance of protective sequence products relative to wild-type abundance of the protective sequence product; and

10 (3) the detection of an aberrant level of protective sequence product activity relative to wild-type protective sequence product activity levels.

Protective nucleic acids can, for example, be used to diagnose a condition, disorder, or disease involving cell death using, for example, the techniques for mutation/polymorphism detection described above in Section 5.1.

15 Mutations at a number of different genetic loci may lead to phenotypes related to conditions, disorders, or diseases involving cell death. Ideally, the treatment of patients suffering from such conditions, disorders, or diseases will be designed to target the particular genetic loci containing the mutation mediating the condition, disorder, or disease. Genetic polymorphisms have been linked to differences in drug effectiveness. Thus, identification of alterations in protective sequence, protein or gene flanking regions can be utilized in
20 pharmacogenetic methods to optimize therapeutic drug treatments.

In one embodiment of the present invention, therefore, alterations, *i.e.*, polymorphisms, in the protective sequence or protein encoded by genes comprising such polymorphisms, are associated with a drug or drugs' efficacy, tolerance or toxicity, and may be used in pharmacogenomic methods to optimize therapeutic drug treatments, including
25 therapeutic drug treatments for one of the conditions, disorders, or diseases described herein contained in Section 5.4.1.1, *e.g.*, central nervous system conditions, disorders, or diseases. Such polymorphisms can be used, for example, to refine the design of drugs by decreasing the incidence of adverse events in drug tolerance studies, *e.g.*, by identifying patient subpopulations of individuals who respond or do not respond to a particular drug therapy in
30 efficacy studies, wherein the subpopulations have a polymorphism associated with drug responsiveness or unresponsiveness. The pharmacogenomic methods of the present invention

also can provide tools to identify new drug targets for designing drugs and to optimize the use of already existing drugs, *e.g.*, to increase the response rate to a drug and/or to identify and exclude non-responders from certain drug treatments (*e.g.*, individuals having a particular polymorphism associated with unresponsiveness or inferior responsiveness to the drug treatment) or to decrease the undesirable side effects of certain drug treatments and/or to identify and exclude individuals with marked susceptibility to such side effects (*e.g.*, individuals having a particular polymorphism associated with an undesirable side effect to the drug treatment).

In an embodiment of the present invention, polymorphisms in the protective sequence or flanking this sequence, or variations in protective sequence expression, or activity, *e.g.*, variations due to altered methylation, differential splicing or post-translational modification of the protective sequence product, may be utilized to identify an individual having a disease or condition resulting from a disorder involving cell death and thus define the most effective and safest drug treatment. Assays such as those described herein may be used to identify such polymorphisms or variations in protective sequence expression or activity. Once a polymorphism in the protective sequence or in a flanking sequence in linkage disequilibrium with a disorder-causing allele, or a variation in protective sequence expression has been identified in an individual, an appropriate drug treatment can be prescribed to the individual.

For the detection of protective sequence mutations or polymorphisms, any nucleated cell can be used as a starting source for genomic nucleic acid. For the detection of protective sequence expression or protective sequence products, any cell type or tissue in which the protective sequence is expressed may be utilized.

Nucleic acid-based detection techniques are described, below, in Section 5.4.1.4. Peptide detection techniques are described, below, in Section 5.4.1.5.

The methods described herein may be performed, for example, by utilizing pre-packaged diagnostic kits. The invention therefore also encompasses kits for detecting the presence of a polypeptide or nucleic acid of the invention in a biological sample (*i.e.*, a test sample). Such kits can be used, *e.g.*, to determine if a subject is suffering from or is at increased risk of developing a condition, disorder, or disease associated with a disorder-causing allele, or aberrant expression or activity of a polypeptide of the invention. For

example, the kit can comprise a labeled compound or agent capable of detecting the polypeptide or mRNA or DNA or protective sequence sequences, *e.g.*, encoding the polypeptide in a biological sample. The kit can comprise further a means for determining the amount of the polypeptide or mRNA in the sample (*e.g.*, an antibody that binds the polypeptide or an oligonucleotide probe that binds to DNA or mRNA encoding the polypeptide). Kits can also include instructions for observing that the tested subject is suffering from, or is at risk of developing, a condition, disorder, or disease associated with aberrant expression of the polypeptide if the amount of the polypeptide or mRNA encoding the polypeptide is above or below a normal level, or if the DNA correlates with presence of an allele which causes a condition, disorder, or disease.

For antibody-based kits, the kit can comprise, for example: (1) a first antibody (*e.g.*, attached to a solid support) which binds to a polypeptide of the invention; and, optionally, (2) a second, different antibody which binds to either the polypeptide or to the first antibody and is conjugated to a detectable agent.

For oligonucleotide-based kits, the kit can comprise, for example: (1) an oligonucleotide (*e.g.*, a detectably labeled oligonucleotide) which hybridizes to a nucleic acid sequence encoding a polypeptide of the invention, or (2) a pair of primers useful for amplifying a nucleic acid molecule encoding a polypeptide of the invention.

The kit also can comprise, for example, one or more buffering agents, preservatives or protein stabilizing agents. The kit also can comprise components necessary for detecting the detectable agent (*e.g.*, an enzyme or a substrate). The kit can contain also a control sample or a series of control samples that can be assayed and compared to the test sample. Each component of the kit usually is enclosed within an individual container and all of the various containers are within a single package along with instructions for observing whether the tested subject is suffering from or is at risk of developing a condition, disorder, or disease associated with polymorphisms which correlate with alleles which cause conditions, disorders, or diseases involving cell death, and/or aberrant levels of mRNA, polypeptides or activity.

Additionally, the application relates to the compositions and methods for the development of screening assays for the identification of compounds, described in Section

5.4.2 below, which interact with or modulate protective sequences, protective sequence products, genes, gene products, and/or their regulatory elements.

5 **5.4.1 Composition and Methods for the Treatment of Conditions, Disorders, or Diseases Involving Cell Death**

 This application relates to compositions and methods for the treatment of conditions, disorders, or diseases involving cell death. Such applications include, but are not limited to, the prophylactic or therapeutic use of protective sequences, protective sequence products, genes, gene products, or the regulatory elements, target sequences, or variants of any of the aforementioned sequences or products, which, when introduced into a cell predisposed to undergo cell death or in the process of dying, prevent, delay, or rescue a cell, cells, tissue, organs, or organisms from dying. The application further relates to the methods and compositions whereby a condition, disorder, or disease involving cell death, including but not limited to, the conditions, disorders, or diseases mentioned in Section 5.4.1.1, may be treated wherein such methods can comprise administering antibodies, antisense molecules or sequences, ribozyme molecules, or other inhibitors or modulators directed against such protective sequences, protective sequence products, genes, gene products, or the regulatory elements, target sequences, or variants of any of the aforementioned sequences or products.

20 The application relates to compositions and methods for those instances whereby the condition, disorder, or disease involving cell death results from protective sequence mutations, such methods can comprise supplying the subject with a nucleic acid molecule encoding an unimpaired protective sequence product such that an unimpaired protective sequence product is expressed and the cell, cells, tissue, organ, organism displaying symptoms of the condition, disorder, or disease is prevented, delayed, or rescued from death.

 In another embodiment of methods for the treatment of conditions, disorders, or diseases involving cell death resulting from protective sequence mutations, such methods can comprise supplying the subject with a cell comprising a nucleic acid molecule which encodes an unimpaired protective sequence product such that the cell expresses the unimpaired protective sequence product and the cell, cells, tissue, organ, or organism displaying symptoms of the condition, disorder, or disease is prevented, delayed, or rescued

from death.

In cases in which a loss of normal protective sequence product function results in the development of a condition, disorder, or disease involving cell death, an increase in protective sequence product activity would facilitate progress towards an asymptomatic state in individuals exhibiting a deficient level of protective sequence expression and/or gene product activity. Methods for enhancing the expression or synthesis of protective sequence product can include, for example, methods such as those described below, in Section 5.4.1.3.

Alternatively, symptoms of a condition, disorder, or disease involving cell death may be prevented, delayed, or rescued by administering a compound which decreases the level of protective sequence expression and/or gene product activity. Methods for inhibiting or reducing the level of protective sequence product synthesis or expression can include, for example, methods such as those described in Section 5.4.1.2.

In cases where the development of a condition, disorder, or disease involving cell death is due to a sequence or gene other than a protective sequence, modulating, including but not limited to, mimicking, agonizing, or antagonizing the expression of a protective sequence and/or the activity of a protective sequence product, or their regulatory elements, can be used for the treatment of the condition, disorder, or disease involving cell death. This is because protective sequences are nucleic acid molecules comprising nucleic acid sequences which, when introduced into a cell predisposed to undergo cell death, prevent, delay, or rescue such cell death relative to a corresponding cell into which no exogenous protective sequence has been introduced.

The proteins and peptides which may be used in the methods of the invention include synthetic (*e.g.*, recombinant or chemically synthesized) proteins and peptides, as well as naturally occurring proteins and peptides. The proteins and peptides may have both naturally occurring and non-naturally occurring amino acid residues (*e.g.*, D-amino acid residues) and/or one or more non-peptide bonds (*e.g.*, imino, ester, hydrazide, semicarbazide, and azo bonds). The proteins or peptides may also contain additional chemical groups (*i.e.*, functional groups) present at the amino and/or carboxy termini, such that, for example, the stability, bioavailability, and/or inhibitory activity of the peptide is enhanced. Exemplary functional groups include hydrophobic groups (*e.g.* carbobenzoxy, dansyl, and t-butyloxycarbonyl groups), an acetyl group, a 9-fluorenylmethoxy-carbonyl group and

macromolecular carrier groups (e.g., lipid-fatty acid conjugates, polyethylene glycol, or carbohydrates) including peptide groups. Additional proteins and peptides which may be used in the methods of the invention include those described in WO 99/59615, which is herein incorporated by reference in its entirety.

5

5.4.1.1 Examples of Conditions, Disorders, or Diseases Involving Cell Death

The types of conditions, disorders, or diseases which can be prevented, delayed, or rescued by the compounds and methods of the present invention include, but are not limited to, those associated with the central nervous system including neurological and psychiatric conditions, disorders, or diseases; those of the peripheral nervous system; conditions, disorders, or diseases caused by physical injury; conditions, disorders, or diseases of the blood vessels or heart; conditions, disorders, or diseases of the respiratory system; neoplastic conditions, disorders, or diseases; conditions, disorders, or diseases of blood cells; conditions, disorders, or diseases of the gastrointestinal tract; conditions, disorders, or diseases of the liver; conditions, disorders, or diseases of the pancreas; conditions, disorders, or diseases of the kidney; conditions, disorders, or diseases of the ureters, urethra or bladder; conditions, disorders, or diseases of the male genital system; conditions, disorders, or diseases of the female genital tract; conditions, disorders, or diseases of the breast; conditions, disorders, or diseases of the endocrine system; conditions, disorders, or diseases of the thymus or pineal gland; conditions, disorders, or diseases of the skin or mucosa; conditions, disorders, or diseases of the musculoskeletal system; conditions, disorders, or diseases causing a fluid or hemodynamic derangement; inherited conditions, disorders, or diseases; conditions, disorders, or diseases of the immune system or spleen; conditions, disorders, or diseases caused by a nutritional disease; and conditions, disorders, or diseases typically occurring in infancy or childhood.

Conditions, disorders, or diseases involving the central nervous system include, but are not limited to, common pathophysiologic complications such as increased intracranial pressure and cerebral herniation, septic embolism, cerebral edema, suppurative endovascularitis and hydrocephalus; infections such as meningitis, acute meningitis, acute lymphocytic meningitis, chronic meningitis, purulent meningitis, syphilitic gumma,

encephalitis, cerebral abscess, epidural abscess, subdural abscess, brain abscess, viral encephalitis, acute viral encephalitis, encephalomeningitis, aseptic meningitis, post-infectious encephalitis, subacute encephalitis, chronic encephalitis, chronic meningitis, chronic encephalomeningitis, slow virus diseases and unconventional agent encephalopathies; 5 protozoal infections such as malaria, toxoplasmosis, amebiasis and trypanosomiasis; rickettsial infections such as typhus and Rocky Mountain spotted fever; metazoal infections such as echinococcosis and cysticercosis; vascular diseases such as ischemic encephalopathy, cerebral infarction, intracranial hemorrhage, intraparenchymal hemorrhage, subarachnoid hemorrhage, mixed intraparenchymal and subarachnoid hemorrhage; conditions involving the 10 eye such as macular degeneration, glaucoma, retinopathy of prematurity, retinitis pigmentosa, diabetic retinopathy, or other traumatic injuries to the retina or optic nerve; trauma such as epidural hematoma, subdural hematoma, parenchymal injuries; tumors such as primary intracranial tumors, astrocytoma, oligodendroglioma, ependymoma, medulloblastoma and meningioma; degenerative diseases such as Alzheimer's disease, Huntington's disease, 15 Parkinsonism, idiopathic Parkinson's disease and motor neuron disease; demyelinating diseases such as multiple sclerosis; nutritional, environmental and metabolic conditions, disorders, or diseases.

Conditions, disorders, or diseases of the peripheral nervous system include, but are not limited to, peripheral neuropathy, acute idiopathic polyneuropathy, diabetic 20 neuropathy and peripheral nerve tumors.

Conditions, disorders, or diseases caused by physical injury include, but are not limited to, the direct, indirect, immediate, or delayed effects of: changes in temperature such as frostbite and thermal burns; an increase in atmospheric pressure such as air blast or immersion blast caused by an explosion; a decrease in atmospheric pressure such as caisson 25 disease or high-altitude hypoxia; mechanical violence from penetrating or non-penetrating traumatic injury; electromechanical energy such as radiation injury from either charged particles or electromagnetic waves; electrocution or non-ionizing radiation such as radio waves, microwaves, laser light or ultrasound.

Conditions, disorders, or diseases of the blood vessels or heart include, but are not limited to, hypertension (high blood pressure), heart failure; ischemic or atherosclerotic heart disease; myocardial infarction; cardiac arrest; hypertensive heart disease; cor 30

pulmonale; valvular heart disease such as that caused by rheumatic fever, aortic valve stenosis, mitral annulus calcification, carcinoid heart disease, nonbacterial thrombotic endocarditis, or nonbacterial verrucous endocarditis; infectious endocarditis caused by organisms including, but not limited to, Streptococcus species, Staphylococcus species, enterococci, pneumococci, gram-negative rods, Candida species, Aspergillus species, or culture-negative endocarditis; congenital heart disease such as atrial septal defect, ventricular septal defect, patent ductus arteriosus, coarctation of the aorta, Tetralogy of Fallot, tricuspid atresia, pulmonary stenosis or atresia, aortic stenosis or atresia, bicuspid aortic valve, or hypoplastic left heart syndrome; cardiomyopathy; pericarditis; pericardial effusion; rheumatoid heart disease; congenital anomalies of the blood vessels; arteriosclerosis including, but not limited to atherosclerosis, Monckeberg's medial calcific stenosis, hyaline arteriosclerosis, or hyperplastic arteriosclerosis; one or more of the vasculidities including, but not limited to, polyarteritis nodosa, hypersensitivity angiitis, Wegener's granulomatosis, giant cell (temporal) arteritis, Takayasu's arteritis, Kawasaki's disease, thromboangiitis obliterans, infectious vasculitis, Raynaud's disease; arteriosclerotic aortic aneurysm; syphilitic aortic aneurysm; dissecting aortic aneurysm; varicose veins; thrombophlebitis; lymphangitis; lymphedema; telangiectases; or arteriovenous malformations (AVM).

Conditions, disorders, or diseases of the respiratory system include, but are not limited to, pulmonary congestion; heart failure; embolism; infarction; pulmonary hypertension; adult respiratory distress syndrome (ARDS); obstructive lung disease; restrictive lung disease; chronic obstructive pulmonary disease; asthma; sarcoidosis; diffuse interstitial or infiltrative lung diseases including, but not limited to, idiopathic pulmonary fibrosis, pneumoconiosis, hypersensitivity pneumonitis, Goodpasture's syndrome, idiopathic pulmonary hemosiderosis, collagen-vascular diseases, or pulmonary eosinophilia; serofibrinous pleuritis; suppurative pleuritis; hemorrhagic pleuritis; pleural effusions; pneumothorax; hemothorax or pneumohemothorax.

Neoplastic conditions, disorders, or diseases include, but are not limited to, benign tumors composed of one parenchymal cell type such as fibromas, myxomas, lipomas, hemangiomas, meningiomas, leiomyomas, adenomas, nevi, moles, or papillomas; benign mixed tumors derived from one germ layer such as a mixed tumor of salivary gland origin; benign mixed tumors derived from more than one germ layer such as a teratoma; primary

malignant tumors or metastases of malignant tumors composed of one parenchymal cell type such as sarcomas, Ewing's tumor, leukemia, myeloma, histiocytosis X, Hodgkin's disease, lymphomas, carcinomas, melanomas, bronchial adenoma, small cell lung cancer, or seminoma; primary malignant tumors or metastases of mixed malignant tumors derived from one germ layer such as Wilms' tumor or malignant mixed salivary gland tumor; primary malignant tumor or metastases of mixed malignant tumors derived from one germ layer such as malignant teratoma or teratocarcinoma; undifferentiated benign tumor or undifferentiated malignant tumor.

Conditions, disorders, or diseases of blood cells include, but are not limited to, anemia due to one or more of the following conditions: acute blood loss, chronic blood loss, hemolytic anemia, sickle cell disease, thalassemia syndromes, autoimmune hemolytic anemia, traumatic anemia, or diminished erythropoiesis from megaloblastic anemia, iron deficiency, aplastic anemia, idiopathic bone marrow failure; polycythemia; hemorrhagic diatheses related to increased vascular fragility; hemorrhagic diatheses related to a reduction in platelets; idiopathic or thrombotic thrombocytopenic purpura; hemorrhagic diatheses related to defective platelet function; hemorrhagic diatheses related to abnormalities in clotting factor(s); disseminated intravascular coagulation (DIC); neutropenia; agranulocytosis; leukocytosis; plasma cell dyscrasias such as myeloma, Waldenstrom's macroglobulinemia, or heavy-chain disease; or histiocytosis.

Conditions, disorders, or diseases of the gastrointestinal tract include, but are not limited to, congenital anomalies such as atresia, fistulas, or stenosis; periodontal disease; periapical disease; xerostomia; necrotizing sialometaplasia; esophageal rings or webs; hernia; Mallory-Weiss syndrome; esophagitis; diverticulosis; diverticulitis; scleroderma; esophageal varices; acute or chronic gastritis; peptic ulcer; gastric erosion or ulceration; ischemic bowel disease; infarction; embolism; Crohn's disease; obstruction from foreign bodies, hernia, adhesion, intussusception, or volvulus; ileus; megacolon; angiodysplasia; ulcerative colitis; pseudomembranous colitis; or polyps.

Conditions, disorders, or diseases of the liver include, but are not limited to, acute hepatic failure due to one of more of metabolic, circulatory, toxic, microbial, or neoplastic causes; chronic hepatic failure due to one or more of metabolic, circulatory, toxic, microbial, or neoplastic causes; hereditary hyperbilirubinemias; infarct; embolism; hepatic

circulation thrombosis or obstruction; fulminant hepatic necrosis; portal hypertension; alcoholic liver disease; post-necrotic cirrhosis; biliary cirrhosis; cirrhosis associated with alpha-1-antitrypsin deficiency; Wilson's disease; or Reye's syndrome.

5 Conditions, disorders, or diseases of the pancreas include, but are not limited to, congenital aberrant pancreas, congenital anomalies of pancreatic ducts, stromal fatty infiltration, pancreatic atrophy, acute hemorrhagic pancreatitis, chronic pancreatitis, chronic calcifying pancreatitis, chronic obstructive pancreatitis, pancreatic pseudocyst, diabetes mellitus, or gestational diabetes.

10 Conditions, disorders, or diseases of the kidney include, but are not limited to, congenital anomalies; polycystic renal disease; dialysis-associated cystic disease; glomerular disease, including, but not limited to, acute glomerulonephritis, acute proliferative glomerulonephritis, rapidly progressive glomerulonephritis, postinfectious rapidly progressive glomerulonephritis, Goodpasture's syndrome, idiopathic rapidly progressive glomerulonephritis, nephrotic syndrome, membranous glomerulonephritis, lipoid nephrosis, 15 focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, focal proliferative glomerulonephritis, chronic glomerulonephritis, or hereditary nephritis; acute tubular necrosis; acute renal failure; tubulointerstitial diseases including, but not limited to, pyelonephritis, drug-induced interstitial nephritis, analgesic nephritis, urate nephropathy, hypercalcemia and nephrocalcinosis, hypokalemic nephropathy, myeloma-induced 20 tubulointerstitial disease, radiation nephritis, immunologically mediated tubulointerstitial disease; hypertension; malignant hypertension; renal artery stenosis; renal diseases secondary to microangiopathic hemolytic anemia; atheroembolic renal disease; sickle cell disease nephropathy; diffuse cortical necrosis; renal infarcts; obstructive uropathy; or urolithiasis.

25 Conditions, disorders, or diseases of the ureters, urethra or bladder include, but are not limited to, congenital anomalies; inflammatory diseases; physical obstruction by causes including, but not limited to calculi, strictures, neoplasia, blood clot, or pregnancy; sclerosing retroperitonitis; acute cystitis; chronic cystitis; interstitial cystitis; emphysematous cystitis; eosinophilic cystitis; encrusted cystitis; fistula; or neurogenic bladder.

30 Conditions, disorders, or diseases of the male genital system include, but are not limited to, congenital anomalies; balanoposthitis; condyloma; phimosis; paraphimosis; dysplastic epithelial lesions; nonspecific epididymitis or orchitis; granulomatous orchitis;

torsion of the testis or its vascular supply; granulomatous prostatitis; acute or chronic prostatitis; or benign prostatic hyperplasia.

5 Conditions, disorders, or diseases of the female genital tract include, but are not limited to, congenital anomalies, lichen scleroses, acute cervicitis, chronic cervicitis, cervical polyps; acute endometritis; chronic endometritis; endometriosis; dysfunctional uterine bleeding; endometrial hyperplasia; senile cystic endometrial atrophy; salpingitis; polycystic ovary disease; pre-eclampsia or eclampsia (toxemia of pregnancy); placentitis; threatened abortion; or ectopic pregnancy.

10 Conditions, disorders, or diseases of the breast include, but are not limited to, congenital anomalies, acute mastitis, chronic mastitis, galactoceles, granulomas, traumatic fat necrosis, mammary duct ectasia, fibrocystic disease, sclerosing adenitis, epithelial hyperplasia, hypertrophy, or gynecomastia.

15 Conditions, disorders, or diseases of the endocrine system include, but are not limited to, congenital anomalies; Sheehan's pituitary necrosis; empty sella syndrome; hyperthyroidism (thyrotoxicosis) from causes including, but not limited to, Graves' disease, toxic multinodular goiter, toxic adenoma, acute or subacute thyroiditis, TSH-secreting tumor, neonatal thyrotoxicosis, iatrogenic thyrotoxicosis; Hashimoto's thyroiditis; hypothyroidism (cretinism or myxedema) from causes including, but not limited to, surgical or radioactive ablation, primary idiopathic myxedema, iodine deficiency, goitrogenic agents, hypopituitarism, hypothalamic lesions, TSH resistance, subacute thyroiditis, or chronic thyroiditis; diffuse nontoxic simple or multinodular goiter; multiple endocrine neoplasia syndromes; primary or secondary hyperparathyroidism; chief cell hyperplasia; clear cell hyperplasia; hypoparathyroidism; pseudo- and pseudopseudohypoparathyroidism; Addison's disease; Waterhouse-Friderichsen syndrome; secondary adrenocortical insufficiency; Cushing's syndrome; Conn's syndrome; or congenital adrenal hyperplasia.

20 Conditions, disorders, or diseases of the skin or mucosa include, but are not limited to, melanocytic proliferative disorders; inflammatory dermatoses including, but not limited to, eczematous dermatitis, urticaria, erythema multiforme, cutaneous necrotizing vasculitis, cutaneous lupus erythematosus, graft-versus-host disease, panniculitis, acne vulgaris, rosacea, lichen planus, lichen sclerosus et atrophicus, pityriasis, psoriasis, or parapsoriasis; blistering diseases including, but not limited to, pemphigus, bullous

pemphigoid, dermatitis herpetiformis, or porphyria.

Conditions, disorders, or diseases of the musculoskeletal system include, but are not limited to, muscular atrophy; segmental necrosis; myositis; muscular dystrophy, including, but not limited to, Duchenne type, Becker type, Fascioscapulohumeral, Limb-
5 Girdle, myotonic dystrophy, or ocular myopathy; congenital myopathies; myasthenia gravis; traumatic myositis ossificans; nodular fasciitis; desmoid tumors; palmar fibromatosis; congenital bone disorders including, but not limited to, osteogenesis imperfecta, achondroplasia, osteopetrosis, osteochondromatosis, endochondromatosis; osteomyelitis; fractures; osteoporosis; osteomalacia; bony changes secondary to hyperparathyroidism;
10 Paget's disease; hypertrophic osteoarthropathy; fibrous dysplasia; or nonossifying fibroma.

Conditions, disorders, or diseases causing a fluid or hemodynamic derangement include, but are not limited to, systemic edema; anasarca; edema from increased hydrostatic pressure including, but not limited to congestive heart failure, cirrhosis of the liver, constrictive pericarditis, venous obstruction; edema from reduced oncotic pressure
15 including, but not limited to, cirrhosis of the liver, malnutrition, protein-losing renal disease, protein-losing gastroenteropathy, protein loss through increased vascular permeability; edema from lymphatic obstruction including, but not limited to, cancer, inflammatory injury, surgical injury, traumatic injury, or radiation injury; edema from increased osmotic tension in the interstitial fluid including, but not limited to, sodium retention from excessive salt intake
20 or increased renal sodium retention, reduced renal perfusion, acute or chronic renal failure, acute or chronic renal insufficiency; edema from increased endothelial permeability including, but not limited to, inflammation, shock, burns, trauma, allergic reaction, immunologic reaction, or adult respiratory distress syndrome; ascites; pericardial effusion; hydrothorax; hyperemia; hemorrhage; mural thrombus or occlusive thrombus diminishing or
25 obstructing vascular flow; phlebothrombosis; blood clot; embolism; thromboembolism; disseminated intravascular coagulation (DIC); amniotic fluid infusion; amniotic fluid embolism; systemic embolism disease; septic embolism; fat embolism; pulmonary embolism; air gas embolism (caisson disease or decompression sickness); anemic (white) infarction; hemorrhagic (red) infarction; cerebral infarction; septic infarction; ischemia; cardiogenic
30 shock from conditions including, but not limited to, myocardial infarction, cardiac arrest, cardiac rupture, cardiac tamponade, pulmonary embolism, cardiac valvular obstruction, or

cardiac arrhythmias; hypovolemic shock from conditions including, but not limited to, hemorrhage, vomiting, diarrhea, diaphoresis, extensive injury to bone or soft tissues, burns, or accumulation of intraperitoneal fluid; shock due to peripheral blood pooling from conditions including, but not limited to, spinal cord injury, general anesthesia, regional anesthesia, local
5 anesthesia, drug-induced ganglionic or adrenergic blockade, gram-negative septicemia, or gram-positive septicemia; anaphylaxis, or disseminated intravascular coagulation (DIC).

Inherited conditions, disorders, or diseases include, but are not limited to, Down's syndrome, Edwards' syndrome, Patau's syndrome, other trisomies, Cri du Chat syndrome, Klinefelter's syndrome, XYY syndrome, Turner's syndrome, Multi-X female
10 syndrome, hermaphroditism or pseudohermaphroditism, Marfan's syndrome, neurofibromatosis, vonHippel-Lindau disease, familial hypercholesterolemia, albinism, alkaptonuria, Fabry's disease, Fragile-X syndrome, Ehlers-Danlos syndromes, inherited neoplastic syndromes, inherited autosomal dominant conditions, Huntington's disease, Alport's disease, sickle-cell disease, thalassemia, tuberous sclerosis, vonWillebrand's disease, polycystic kidney disease,
15 Pompe's disease, GM1-gangliosidosis; Tay-Sachs disease, Sandhoff-Jatzkewitz disease, metachromatic leukodystrophy, multiple sulfatase deficiency, Krabbe's disease, Gaucher's disease, Niemann-Pick disease, all types of mucopolysaccharidoses, I-cell disease, Hurler's polydystrophy, fucosidosis, mannosidosis, aspartylglycosaminuria, Wolman's disease, or acid phosphatase deficiency, inherited autosomal recessive conditions, inherited sex-linked
20 conditions.

Conditions, disorders, or diseases of the immune system or spleen include, but are not limited to, Type I hypersensitivity conditions (anaphylaxis and other basophil or mast cell mediated conditions), Type II hypersensitivity conditions (cytotoxic conditions involving phagocytosis or lysis of target cell), Type III hypersensitivity conditions (immune complex
25 conditions involving antigen-antibody complexes), Type IV hypersensitivity conditions (cell-mediated conditions), transplant rejection, systemic lupus erythematosus, Sjogren's syndrome, CREST, scleroderma, polymyositis-dermatomyositis, mixed connective tissue disease, polyarteritis nodosa, amyloidosis, X-linked agammaglobulinemia, common variable immunodeficiency, isolated IgA deficiency, DiGeorge's syndrome, severe combined
30 immunodeficiency, Wiscott-Aldrich syndrome, infection with HIV virus, acquired immune deficiency syndrome (AIDS), congenital anomalies of the immune system, hypersplenism,

splenomegaly, congenital anomalies of the spleen, congestive splenomegaly, infarcts, or splenic rupture.

Conditions, disorders, or diseases caused by a nutritional disease include, but are not limited to, marasmus, kwashiorkor, fat-soluble vitamin deficiency or toxicity (Vitamins A, D, E, or K), water-soluble vitamin deficiency or toxicity (thiamine, riboflavin, niacin, pyridoxine, folate, cobalamin, Vitamin C), mineral deficiency or toxicity (iron, calcium, magnesium, sodium, potassium, chloride, zinc, copper, iodine, cobalt, chromium, selenium, nickel, vanadium, manganese, molybdenum, rickets, osteomalacia, beriberi, hypoprothrombinemia, pellagra, megaloblastic anemia, scurvy, pernicious anemia, lack of gastric intrinsic factor, removal or pathophysiological functioning in the terminal ileum, microcytic anemia, or obesity.

Conditions, disorders, or diseases typically occurring in infancy or childhood include, but are not limited to, preterm birth, congenital malformations from genetic causes, congenital malformations from infectious causes, congenital malformations from toxic or teratogenic causes, congenital malformations from radiation, congenital malformations from idiopathic causes, small for gestational age infants, perinatal trauma, perinatal asphyxia, perinatal ischemia or hypoxia, birth injury, intracranial hemorrhage, deformations, respiratory distress syndrome of the newborn, atelectasis, hemolytic disease of the newborn, kernicterus, hydrops fetalis, congenital anemia of the newborn, icterus gravis, phenylketonuria, galactosemia, cystic fibrosis, hamartoma, or choristoma.

In another embodiment, the compounds and methods of the invention can be used to treat infections that cause cell death. The infections may be caused by bacteria; viruses; members of the family rickettsiae or chlamydia; fungi, yeast, hyphae or pseudohyphae; prions; protozoas; or metazoas.

Examples of aerobic or anaerobic bacteria which may cause such infections include, but are not limited to, gram-positive cocci, gram-positive bacilli (gram-positive rods), gram-negative cocci, gram-negative bacilli (gram-negative rods), Mycoplasma species, Ureaplasma species, Treponema species, Leptospira species, Borrelia species, Vibrio species, Mycobacteria species, members of Actinomycetes or L-forms (cell-wall deficient forms).

Examples of DNA, RNA or both DNA and RNA viruses which may cause such infections include, but are not limited to, members of the families adenoviridae,

parvoviridae, papovaviridae, herpesviridae, poxviridae, picornaviridae, orthomyxoviridae, paramyxoviridae, rhabdoviridae, bunyaviridae, arenaviridae, coronaviridae, retroviridae, reoviridae, togaviridae and caliciviridae.

5 Examples of members of the families rickettsiae or chlamydiae which may cause such infections include, but are not limited to, Rickettsia species, Rochalimaea species, Coxiella species or Chlamydia species.

Examples of fungi, yeast, hyphae or pseudohyphae which may cause such infections include, but are not limited to, members of Ascomycota, Basidiomycota, Zygomycota, or Deuteromycota (Fungi Imperfecti); Candida species, Cryptococcus species, 10 Torulopsis species, Rhodotorula species, Sporothrix species, Phialophora species, Cladosporium species, Xylohypha species, Blastomyces species, Histoplasma species, Coccidioides species, Paracoccidioides species, Geotrichum species, Aspergillus species, Rhizopus species, Mucor species, Pseudoallescheria species or Absidia species.

Examples of prions which may cause such infections include, but are not 15 limited to, the causative agent of Creutzfeldt-Jakob Disease, the causative agent of Gerstmann-Straussler-Scheinker Disease, the causative agent of fatal familial insomnia, the causative agent of kuru, and the causative agent of bovine spongiform encephalopathy.

Examples of protozoa at any point in their life cycle which may cause such infections include, but are not limited to, Entamoeba species, Naegleria species, 20 Acanthamoeba species, Pneumocystis species, Balantidium species, members of order Leptomyxida, Plasmodium species, Toxoplasma species, Leishmania species and Trypanosoma species.

Examples of metazoa at any point in their life cycle which may cause such infections include, but are not limited to, members of Platyhelminthes such as the organisms 25 in Cestoda (tapeworms) or Trematoda (flukes); or members of Aschelminthes such as the organisms in Acanthocephala, Chaetognatha, Cyclophora, Gastrotricha, Nematoda or Rotifera.

In a further embodiment, the compounds and methods of the invention can be used to treat infections or disorders which cause cell death in organ systems including, but not 30 limited to, blood vessels, heart, red blood cells, white blood cells, lymph nodes, spleen, respiratory system, oral cavity, gastrointestinal tract, liver and biliary tract, pancreas, kidney,

lower urinary tract, upper urinary tract and bladder, male sexual organs and genitalia, female sexual organs and genitalia, breast, thyroid gland, adrenal gland, parathyroid gland, skin, musculoskeletal system, bone marrow or bones.

5 In a further embodiment, the compounds and methods of the invention can be used to treat further physiological impacts on organs caused by the infections which induce cell death including, but not limited to, fever equal to or greater than 101.5 degrees Fahrenheit, a decrease or increase in pulse rate by more than 20 beats per minute, a decrease or increase in supine systolic blood pressure by more than 30 millimeters of mercury, an increase or decrease in respiratory rate by more than 8 breaths per minute, an increase or decrease in blood pH by more than 0.10 pH units, an increase or decrease in one or more serum electrolytes outside of the clinical laboratory's usual reference range, an increase or decrease in the partial pressure of arterial oxygen or carbon dioxide outside of the clinical laboratory's usual reference range, an increase or decrease in white or red blood cells outside of the laboratory's usual reference range, an acute confusional state such as delirium where delirium is defined by the American Psychiatric Association's DSM-IV Manual or a diminished level of consciousness or attention.

5.4.1.2 Modulatory Antisense, Ribozyme and Triple Helix Approaches

20 In another embodiment, the types of conditions, disorders, or diseases involving cell death which may be prevented, delayed, or rescued by modulating protective sequence expression, protective sequence product activity, or their regulatory elements by using protective sequences in conjunction with well-known antisense, gene "knock-out,"
25 ribozyme and/or triple helix methods, are described. Among the compounds which may exhibit the ability to modulate the activity, expression or synthesis of the protective sequence, the protective sequence product, or its regulatory elements, including the ability to prevent, delay, or rescue a cell, cells, tissue, organ, or organism from the symptoms of a condition, disorder, or disease involving cell death are antisense, ribozyme and triple helix molecules.
30 Such molecules may be designed to modulate, reduce or inhibit either unimpaired, or if appropriate, mutant protective sequence activity. Techniques for the production and use of such molecules are well known to those of skill in the art.

Antisense RNA and DNA molecules act to directly block the translation of mRNA by hybridizing to targeted mRNA and preventing protein translation. Antisense approaches involve the design of oligonucleotides which are complementary to a protective sequence mRNA. The antisense oligonucleotides will bind to the complementary protective sequence mRNA transcripts and prevent translation. Absolute complementarity, although preferred, is not required.

A sequence "complementary" to a portion of an RNA, as referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double-stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the longer the hybridizing nucleic acid, the more base mismatches with an RNA it may contain and still form a stable duplex (or triplex, as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

In one embodiment, oligonucleotides complementary to non-coding regions of the protective sequence of interest could be used in an antisense approach to inhibit translation of endogenous mRNA. Antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50 nucleotides in length. In specific aspects, the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least 50 nucleotides.

Regardless of the choice of target sequence, it is preferred that *in vitro* studies are first performed to quantitate the ability of the antisense oligonucleotide to inhibit protective sequence expression. It is preferred that these studies utilize controls that distinguish between antisense gene inhibition and nonspecific biological effects of oligonucleotides. It is also preferred that these studies compare levels of the cerebral RNA or protein with that of an internal control RNA or protein. Additionally, it is envisioned that results obtained using the antisense oligonucleotide are compared with those obtained using a control oligonucleotide. It is preferred that the control oligonucleotide is of approximately the same length as the test oligonucleotide and that the nucleic acid of the oligonucleotide

differs from the antisense sequence no more than is necessary to prevent specific hybridization to the target sequence.

The oligonucleotides can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, *e.g.*, Letsinger, *et al.*, 1989, *Proc. Natl. Acad. Sci. U.S.A.* 86:6553-6556; Lemaitre, *et al.*, 1987, *Proc. Natl. Acad. Sci. U.S.A.* 84:648-652; PCT Publication No. WO88/09810, published December 15, 1988) or the blood-brain barrier (see, *e.g.*, PCT Publication No. WO89/10134, published April 25, 1988), hybridization-triggered cleavage agents (see, *e.g.*, Krol *et al.*, 1988, *BioTechniques* 6:958-976) or intercalating agents (see, *e.g.*, Zon, 1988, *Pharm. Res.* 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, *e.g.*, a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including but not limited to 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including but not limited to arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group consisting of a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

5 In yet another embodiment, the antisense oligonucleotide is an a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual b-units, the strands run parallel to each other (Gautier, *et al.*, 1987, *Nucl. Acids Res.* 15:6625-6641). The oligonucleotide is a 2'-O-methylribonucleotide (Inoue, *et al.*, 1987, *Nucl. Acids Res.* 15:6131-6148), or a chimeric
10 RNA-DNA analogue (Inoue, *et al.*, 1987, *FEBS Lett.* 215:327-330).

Oligonucleotides of the invention may be synthesized by standard methods known in the art, *e.g.*, by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein, *et al.* (1988, *Nucl. Acids Res.*
15 16:3209), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin, *et al.*, 1988, *Proc. Natl. Acad. Sci. U.S.A.* 85:7448-7451), *etc.*

While antisense nucleotides complementary to the protective sequence coding region sequence could be used, those complementary to the transcribed, untranslated region are most preferred.

20 Antisense molecules should be delivered to cells that express the protective sequence *in vivo*. A number of methods have been developed for delivering antisense DNA or RNA to cells; *e.g.*, antisense molecules can be injected directly into the tissue site, or modified antisense molecules, designed to target the desired cells (*e.g.*, antisense linked to peptides or antibodies which specifically bind receptors or antigens expressed on the target
25 cell surface) can be administered systemically.

A preferred approach to achieve intracellular concentrations of the antisense sufficient to suppress translation of endogenous mRNAs utilizes a recombinant DNA construct in which the antisense oligonucleotide is placed under the control of a strong pol III or pol II promoter. The use of such a construct to transfect target cells in the patient will
30 result in the transcription of sufficient amounts of single stranded RNAs which will form complementary base pairs with the endogenous protective sequence transcripts and thereby

prevent translation of the protective sequence mRNA. For example, a vector can be introduced *e.g.*, such that it is taken up by a cell and directs the transcription of an antisense RNA. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in mammalian cells. Expression of the sequence encoding the antisense RNA can be by any promoter known in the art to act in mammalian, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include but are not limited to: the SV40 early promoter region (Bernoist and Chambon, 1981, *Nature* 290:304-310), the promoter contained in the 3'-long terminal repeat of Rous sarcoma virus (Yamamoto, *et al.*, 1980, *Cell* 22:787-797), the herpes thymidine kinase promoter (Wagner, *et al.*, 1981, *Proc. Natl. Acad. Sci. U.S.A.* 78:1441-1445), the regulatory sequences of the metallothionein gene (Brinster, *et al.*, 1982, *Nature* 296:39-42), etc. Any type of plasmid, cosmid, YAC or viral vector can be used to prepare the recombinant DNA construct that can be introduced directly into the tissue site. Alternatively, viral vectors can be used that selectively infect the desired tissue, in which case administration may be accomplished by another route (*e.g.*, systemically).

Ribozyme molecules designed to catalytically cleave target gene mRNA transcripts can also be used to prevent translation of target gene mRNA and, therefore, expression of target gene product. (See, *e.g.*, PCT International Publication WO90/11364, published October 4, 1990; Sarver, *et al.*, 1990, *Science* 247, 1222-1225).

Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. (For a review, see Rossi, 1994, *Current Biology* 4:469-471). The mechanism of ribozyme action involves sequence specific hybridization of the ribozyme molecule to complementary target RNA, followed by an endonucleolytic cleavage event. The composition of ribozyme molecules must include one or more sequences complementary to the target gene mRNA, and must include the well known catalytic sequence responsible for mRNA cleavage. For this sequence, see, *e.g.*, U.S. Patent No. 5,093,246, which is incorporated herein by reference in its entirety.

While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy target gene mRNAs, the use of hammerhead ribozymes is preferred.

Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions which form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Myers, 5 1995, *Molecular Biology and Biotechnology: A Comprehensive Desk Reference*, VCH Publishers, New York, (see especially Figure 4, page 833) and in Haseloff and Gerlach, 1988, *Nature*, 334:585-591, which is incorporated herein by reference in its entirety.

Preferably the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the target gene mRNA, *i.e.*, to increase efficiency and minimize the 10 intracellular accumulation of non-functional mRNA transcripts.

The ribozymes of the present invention also include RNA endoribonucleases (hereinafter "Cech-type ribozymes") such as the one which occurs naturally in *Tetrahymena thermophila* (known as the IVS, or L-19 IVS RNA) and which has been extensively described by Thomas Cech and collaborators (Zaug, *et al.*, 1984, *Science*, 224:574-578; Zaug and Cech, 15 1986, *Science*, 231:470-475; Zaug, *et al.*, 1986, *Nature*, 324:429-433; published International patent application No. WO 88/04300 by University Patents Inc.; Been and Cech, 1986, *Cell*, 47:207-216). The Cech-type ribozymes have an eight base pair active site that hybridizes to a target RNA sequence whereafter cleavage of the target RNA takes place. The invention encompasses those Cech-type ribozymes that target eight base-pair active site sequences that 20 are present in the target gene.

As in the antisense approach, the ribozymes can be composed of modified oligonucleotides (*e.g.*, for improved stability, targeting, *etc.*) and should be delivered to cells that express the target gene *in vivo*. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive pol III or pol II 25 promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy endogenous target gene messages and inhibit translation. Because ribozymes, unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

Endogenous target gene expression can also be reduced by inactivating or 30 "knocking out" the target gene or its promoter using targeted homologous recombination (*e.g.*, see Smithies, *et al.*, 1985, *Nature* 317:230-234; Thomas and Capecchi, 1987, *Cell*

51:503-512; Thompson, *et al.*, 1989, *Cell* 5:313-321; each of which is incorporated by reference herein in its entirety). For example, a mutant, non-functional target gene (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous target gene (either the coding regions or regulatory regions of the target gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells which express the target gene *in vivo*. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the target gene. Such approaches are particularly suited in the agricultural field where modifications to ES (embryonic stem) cells can be used to generate animal offspring with an inactive target gene (*e.g.*, see Thomas and Capecchi, 1987 and Thompson, 1989, *supra*). However this approach can be adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors.

Alternatively, endogenous target gene expression can be reduced by targeting deoxyribonucleotide sequences complementary to the regulatory region of the target gene (*i.e.*, the target gene promoter and/or enhancers) to form triple helical structures which prevent transcription of the target gene in target cells in the body. (See generally, Helene, 1991, *Anticancer Drug Des.*, 6(6):569-584; Helene, *et al.*, 1992, *Ann. N.Y. Acad. Sci.*, 660:27-36; and Maher, 1992, *Bioassays* 14(12):807-815).

Nucleic acid molecules to be used in triple helix formation for the inhibition of transcription should be single stranded and composed of deoxynucleotides. The base composition of these oligonucleotides must be designed to promote triple helix formation via Hoogsteen base pairing rules, which generally require sizable stretches of either purines or pyrimidines to be present on one strand of a duplex. Nucleic acids may be pyrimidine-based, which will result in TAT and CGC⁺ triplets across the three associated strands of the resulting triple helix. The pyrimidine-rich molecules provide base complementarity to a purine-rich region of a single strand of the duplex in a parallel orientation to that strand. In addition, nucleic acid molecules may be chosen which are purine-rich, for example, contain a stretch of G residues. These molecules will form a triple helix with a DNA duplex that is rich in GC pairs, in which the majority of the purine residues are located on a single strand of the targeted duplex, resulting in GGC triplets across the three strands in the triplex.

Alternatively, the potential sequences that can be targeted for triple helix formation may be increased by creating a so-called "switchback" nucleic acid molecule. Switchback molecules are synthesized in an alternating 5'-3', 3'-5' manner, such that they base pair with first one strand of a duplex and then the other, eliminating the necessity for a sizable stretch of either purines or pyrimidines to be present on one strand of a duplex.

In instances wherein the antisense, ribozyme, and/or triple helix molecules described herein are utilized to inhibit mutant gene expression, it is possible that the technique may so efficiently reduce or inhibit the transcription (triple helix) and/or translation (antisense, ribozyme) of mRNA produced by normal target gene alleles which the possibility may arise wherein the concentration of normal target gene product present may be lower than is necessary for a normal phenotype. In such cases, to ensure that substantially normal levels of target gene activity are maintained, therefore, nucleic acid molecules which encode and express target gene polypeptides exhibiting normal target gene activity may, be introduced into cells via gene therapy methods such as those described, below, in Section 5.4.1.3 which do not contain sequences susceptible to whatever antisense, ribozyme, or triple helix treatments are being utilized. Alternatively, in instances whereby the target gene encodes an extracellular protein, it may be preferable to co-administer normal target gene protein in order to maintain the requisite level of target gene activity.

Anti-sense RNA and DNA, ribozyme, and triple helix molecules of the invention may be prepared by any method known in the art for the synthesis of DNA and RNA molecules, as discussed above. These include techniques for chemically synthesizing oligodeoxyribonucleotides and oligoribonucleotides well known in the art such as for example solid-phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by *in vitro* and *in vivo* transcription of DNA sequences encoding the antisense RNA molecule. Such DNA sequences may be incorporated into a wide variety of vectors that incorporate suitable RNA polymerase promoters such as the T7 or SP6 polymerase promoters. Alternatively, antisense cDNA constructs that synthesize antisense RNA constitutively or inducibly, depending on the promoter used, can be introduced stably into cell lines.

5.4.1.3 Gene Replacement Therapy

Protective nucleic acid sequences, described above in Section 5.1, can be utilized for transferring recombinant protective nucleic acid sequences to cells and expressing said sequences in recipient cells. Such techniques can be used, for example, in marking cells or for the treatment of a condition, disorder, or disease involving cell death. Such treatment can be in the form of gene replacement therapy. Specifically, one or more copies of a normal protective sequence or a portion of the protective sequence which directs the production of a protective sequence product exhibiting normal protective sequence function, may be inserted into the appropriate cells within a patient, using vectors which include, but are not limited to adenovirus, adeno-associated virus and retrovirus vectors, in addition to other particles which introduce DNA into cells, such as liposomes.

Because the protective sequence of the invention may be expressed in the brain, such gene replacement therapy techniques should be capable of delivering protective sequences to these cell types within patients. Thus, in one embodiment, techniques which are well known to those of skill in the art (see, *e.g.*, PCT Publication No. WO89/10134, published April 25, 1988) can be used to enable protective sequences to cross the blood-brain barrier readily and to deliver the sequences to cells in the brain. With respect to delivery which is capable of crossing the blood-brain barrier, viral vectors such as, for example, those described above, are preferable.

In another embodiment, techniques for delivery involve direct administration, *e.g.*, by stereotactic delivery of such protective sequences to the site of the cells in which the protective sequences are to be expressed.

Methods for introducing genes for expression in mammalian cells are well known in the field. Generally, for such gene therapy methods, the nucleic acid is directly administered *in vivo* into a target cell or a transgenic mouse that expresses SP-10 promoter operably linked to a reporter gene. This can be accomplished by any methods known in the art, *e.g.*, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, *e.g.*, by infection using a defective or attenuated retroviral or other viral vector (see U.S. Patent No. 4,980,286), by direct injection of naked DNA, by use of microparticle bombardment (*e.g.*, a gene gun; Biolistic, Dupont), by coating with lipids or cell-surface receptors or transfecting agents, by encapsulation in

liposomes, microparticles, or microcapsules, by administering it in linkage to a peptide which is known to enter the nucleus, or by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see e.g., Wu and Wu, 1987, J. Biol. Chem. 262:4429-4432), which can be used to target cell types specifically expressing the receptors. In another embodiment, a
5 nucleic acid-ligand complex can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted *in vivo* for cell specific uptake and expression, by targeting a specific receptor (see, e.g., PCT Publications WO 92/06180 dated April 16, 1992; WO 92/22635 dated December 23, 1992; WO92/20316 dated November 26,
10 1992; WO93/14188 dated July 22, 1993; WO 93/20221 dated October 14, 1993).

Additional methods which may be utilized to increase the overall level of protective sequence expression and/or gene product activity include using targeted homologous recombination methods, discussed in Section 5.2, above, to modify the expression characteristics of an endogenous protective sequence in a cell or microorganism
15 by inserting a heterologous DNA regulatory element such that the inserted regulatory element is operatively linked with the endogenous protective sequence in question. Targeted homologous recombination can thus be used to activate transcription of an endogenous protective sequence which is "transcriptionally silent", *i.e.*, is not normally expressed or is normally expressed at very low levels, or to enhance the expression of an endogenous
20 protective sequence which is normally expressed.

Further, the overall level of protective sequence expression and/or gene product activity may be increased by the introduction of appropriate protective sequence-expressing cells, preferably autologous cells, into a patient at positions and in numbers which are sufficient to ameliorate the symptoms of a condition, disorder, or disease involving cell
25 death. Such cells may be either recombinant or non-recombinant.

Among the cells that can be administered to increase the overall level of protective sequence expression in a patient are normal cells, preferably brain cells, which express the protective sequence. Alternatively, cells, preferably autologous cells, can be engineered to express protective sequences, and may then be introduced into a patient in
30 positions appropriate for the amelioration of the symptoms of a condition, disorder, or disease involving cell death. Alternately, cells which express an unimpaired protective sequence and

which are from a MHC matched individual can be utilized, and may include, for example, brain cells. The expression of the protective sequences is controlled by the appropriate gene regulatory sequences to allow such expression in the necessary cell types. Such gene regulatory sequences are well known to the skilled artisan. Such cell-based gene therapy techniques are well known to those skilled in the art, see, *e.g.*, Anderson, U.S. Patent No. 5,399,349.

When the cells to be administered are non-autologous cells, they can be administered using well-known techniques that prevent a host immune response against the introduced cells from developing. For example, the cells may be introduced in an encapsulated form that, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Additionally, compounds, such as those identified via techniques such as those described, in Section 5.4.2, which are capable of modulating protective sequences, protective sequence product activity, or their regulatory sequences can be administered using standard techniques which are well known to those of skill in the art. In instances in which the compounds to be administered are to involve an interaction with brain cells, the administration techniques should include well known methods that allow for a crossing of the blood-brain barrier.

5.4.1.4 Detection of Protective Nucleic Acid Molecules

A variety of methods can be employed to screen for the presence of protective sequence-specific mutations or polymorphisms (including polymorphisms flanking protective sequences) and to detect and/or assay levels of protective nucleic acid sequences.

Mutations or polymorphisms within or flanking the protective sequences can be detected by utilizing a number of techniques. Nucleic acid from any nucleated cell can be used as the starting point for such assay techniques, and may be isolated according to standard nucleic acid preparation procedures that are well known to those of skill in the art.

Protective nucleic acid sequences may be used in hybridization or amplification assays of biological samples to detect abnormalities involving protective sequence structure, including point mutations, insertions, deletions, inversions, translocations

and chromosomal rearrangements. Such assays may include, but are not limited to, Southern analyses, single-stranded conformational polymorphism analyses (SSCP) and PCR analyses.

Diagnostic methods for the detection of protective sequence-specific mutations or polymorphisms can involve for example, contacting and incubating nucleic acids obtained from a sample, *e.g.*, derived from a patient sample or other appropriate cellular source with one or more labeled nucleic acid reagents including recombinant DNA molecules, cloned genes or degenerate variants thereof, such as described in Section 5.1, above, under conditions favorable for the specific annealing of these reagents to their complementary sequences within or flanking the protective sequence. The diagnostic methods of the present invention further encompass contacting and incubating nucleic acids for the detection of single nucleotide mutations or polymorphisms of the protective sequence. Preferably, these nucleic acid reagent sequences within the protective sequence are 15 to 30 nucleotides in length.

After incubation, all non-annealed nucleic acids are removed from the reaction. The presence of nucleic acids that have hybridized, if any such molecules exist, is then detected. Using such a detection scheme, the nucleic acid from the cell type or tissue of interest can be immobilized, for example, to a solid support such as a membrane, or a plastic surface such as that on a microtiter plate or polystyrene beads. In this case, after incubation, non-annealed, labeled nucleic acid reagents of the type described in Section 5.1 are easily removed. Detection of the remaining, annealed, labeled nucleic acid reagents is accomplished using standard techniques well known to those skilled in the art. The protective sequences of the invention to which the nucleic acid reagents have annealed can be compared to the annealing pattern expected from a normal protective sequence of the invention in order to determine whether a protective sequence mutation is present.

In a preferred embodiment, protective sequence mutations or polymorphisms can be detected by using a microassay of nucleic acid sequences of the invention immobilized to a substrate or "gene chip" (see, *e.g.* Cronin, et al., 1996, Human Mutation 7:244-255). Alternative diagnostic methods for the detection of protective sequence-specific nucleic acid molecules (or flanking sequences), in patient samples or other appropriate cell sources, may involve their amplification, *e.g.*, by PCR (the experimental embodiment set forth in Mullis, 1987, U.S. Patent No. 4,683,202), followed by the analysis of the amplified molecules using

techniques well known to those of skill in the art, such as, for example, those listed above. The resulting amplified sequences can be compared to those which would be expected if the nucleic acid being amplified contained only normal copies of the protective sequence in order to determine whether a protective sequence mutation or polymorphism in linkage disequilibrium with a disease-causing allele exists.

Among those nucleic acid sequences that are preferred for such amplification-related diagnostic screening analyses are oligonucleotide primers that amplify exon sequences. The sequences of such oligonucleotide primers are, therefore, preferably derived from cerebral intron sequences so that the entire exon, or coding region, can be analyzed as discussed below. Primer pairs useful for amplification of cerebral exons are preferably derived from adjacent introns. Appropriate primer pairs can be chosen such that each of the cerebral exons present within the gene will be amplified. Primers for the amplification of exons can be routinely designed by one of ordinary skill.

Additional nucleic acid sequences which are preferred for such amplification-related analyses are those which will detect the presence of a polymorphism which differs from the sequence depicted in the Figures. Such polymorphisms include ones that represent mutations associated with a condition, disorder, or disease involving cell death.

Amplification techniques are well known to those of skill in the art and can routinely be utilized in connection with primers such as those described above. In general, hybridization conditions can be as follows: In general, for probes between 14 and 70 nucleotides in length, the melting temperature T_m is calculated using the formula: $T_m(^{\circ}\text{C}) = 81.5 + 16.6(\log[\text{monovalent cations}]) + 0.41(\% \text{ G+C}) - (500/N)$ where N is the length of the probe. If the hybridization is carried out in a solution containing formamide, the melting temperature is calculated using the equation $T_m(^{\circ}\text{C}) = 81.5 + 16.6(\log[\text{monovalent cations}]) + 0.41(\% \text{ G+C}) - (0.61\% \text{ formamide}) - (500/N)$ where N is the length of the probe. Additionally, well-known genotyping techniques can be performed to identify individuals carrying protective sequence mutations. Such techniques include, for example, the use of restriction fragment length polymorphisms (RFLPs), which involve sequence variations in one of the recognition sites for the specific restriction enzyme used.

Further, improved methods for analyzing DNA polymorphisms, which can be utilized for the identification of protective sequence-specific mutations, have been described

which capitalize on the presence of variable numbers of short, tandemly repeated DNA sequences between the restriction enzyme sites. For example, Weber (U.S. Pat. No. 5,075,217) describes a DNA marker based on length polymorphisms in blocks of (dC-dA)_n-(dG-dT)_n short tandem repeats. The average separation of (dC-dA)_n-(dG-dT)_n blocks is estimated to be 30,000-60,000 bp. Markers which are so closely spaced exhibit a high frequency of co-inheritance, and are extremely useful in the identification of genetic mutations, such as, for example, mutations within the protective sequence of the invention, and the diagnosis of diseases and disorders related to mutations of the protective sequences of the invention.

Also, Caskey *et al.* (U.S. Pat.No. 5,364,759) describe a DNA profiling assay for detecting short tri- and tetra nucleotide repeat sequences. The process includes extracting the DNA of interest, amplifying the extracted DNA and labeling the repeat sequences to form a genotypic map of the individual's DNA.

Other methods well known in the art may be used to identify single nucleotide polymorphisms (SNPs), including biallelic SNPs or biallelic markers which have two alleles, both of which are present at a fairly high frequency in a population. Conventional techniques for detecting SNPs include, *e.g.*, conventional dot blot analysis, single stranded conformational polymorphism (SSCP) analysis (see, *e.g.*, Orita *et al.*, 1989, *Proc. Natl. Acad. Sci. USA* 86:2766-2770), denaturing gradient gel electrophoresis (DGGE), heteroduplex analysis, mismatch cleavage detection and other routine techniques well known in the art (see, *e.g.*, Sheffield *et al.*, 1989, *Proc. Natl. Acad. Sci.* 86:5855-5892; Grompe, 1993, *Nature Genetics* 5:111-117). Alternative, preferred methods of detecting and mapping SNPs involve microsequencing techniques wherein an SNP site in a target DNA is detecting by a single nucleotide primer extension reaction (see, *e.g.*, Goelet *et al.*, PCT Publication No.

WO92/15712; Mundy, U.S. Patent No. 4,656,127; Vary and Diamond, U.S. Patent No. 4,851,331; Cohen *et al.*, PCT Publication No. WO91/02087; Chee *et al.*, PCT Publication No. WO95/11995; Landegren *et al.*, 1988, *Science* 241:1077-1080; Nicerson *et al.*, 1990, *Proc. Natl. Acad. Sci. U.S.A.* 87:8923-8927; Pastinen *et al.*, 1997, *Genome Res.* 7:606-614; Pastinen *et al.*, 1996, *Clin. Chem.* 42:1391-1397; Jalanko *et al.*, 1992, *Clin. Chem.* 38:39-43; Shumaker *et al.*, 1996, *Hum. Mutation* 7:346-354; Caskey *et al.*, PCT Publication No. WO 95/00669).

The level of protective sequence expression also can be assayed. For example, RNA from a cell type or tissue known, or suspected, to express the protective sequence, such as brain, may be isolated and tested utilizing hybridization or PCR techniques such as are described, above. The isolated cells can be derived from cell culture or from a patient. The analysis of cells taken from culture may be a necessary step in the assessment of cells to be used as part of a cell-based gene therapy technique or, alternatively, to test the effect of compounds on the expression of the protective sequence. Such analyses may reveal both quantitative and qualitative aspects of the expression pattern of the protective sequence, including activation or inactivation of protective sequence expression.

In one embodiment of such a detection scheme, a cDNA molecule is synthesized from an RNA molecule of interest (*e.g.*, by reverse transcription of the RNA molecule into cDNA). A sequence within the cDNA is then used as the template for a nucleic acid amplification reaction, such as a PCR amplification reaction, or the like. The nucleic acid reagents used as synthesis initiation reagents (*e.g.*, primers) in the reverse transcription and nucleic acid amplification steps of this method are chosen from among the protective sequence nucleic acid reagents described in Section 5.1. The preferred lengths of such nucleic acid reagents are at least 9-30 nucleotides. For detection of the amplified product, the nucleic acid amplification may be performed using radioactively or non-radioactively labeled nucleotides. Alternatively, enough amplified product may be made such that the product may be visualized by standard ethidium bromide staining or by utilizing any other suitable nucleic acid staining method.

Additionally, it is possible to perform such protective sequence expression assays "*in situ*", *i.e.*, directly upon tissue sections (fixed and/or frozen) of patient tissue obtained from biopsies or resections, such that no nucleic acid purification is necessary. Nucleic acid reagents such as those described in Section 5.1 may be used as probes and/or primers for such *in situ* procedures (see, for example, Nuovo, G.J., 1992, "PCR In Situ Hybridization: Protocols And Applications", Raven Press, NY).

Alternatively, if a sufficient quantity of the appropriate cells can be obtained, standard Northern blot analysis can be performed to determine the level of mRNA expression of the protective sequence.

5.4.1.5 Detection of Protective Sequence Products

Protective sequence products of the invention, including both wild-type and mutant protective sequence products, conserved variants and polypeptide fragments thereof, which are discussed, above, in Section 5.2, may be detected using antibodies which are directed against such gene products. Such antibodies, which are discussed in Section 5.3, above, may thereby be used as diagnostics and prognostics for a condition, disorder, or disease involving cell death. Such methods may be used to detect abnormalities in the level of protective sequence expression or of protective sequence product synthesis, or abnormalities in the structure, temporal expression and/or physical location of protective sequence product. The antibodies and immunoassay methods described herein have, for example, important *in vitro* applications in assessing the efficacy of treatments for conditions, disorders, or diseases involving cell death. Antibodies, or fragments of antibodies, such as those described below, may be used to screen potentially therapeutic compounds *in vitro* to determine their effects on protective sequence expression and protective sequence product production. The compounds which have beneficial effects on conditions, disorders, or diseases involving cell death can thereby be identified, and a therapeutically effective dose determined.

In vitro immunoassays may also be used, for example, to assess the efficacy of cell-based gene therapy for a condition, disorder, or disease involving cell death. Antibodies directed against protective sequence products may be used *in vitro* to determine, for example, the level of protective sequence expression achieved in cells genetically engineered to produce the protective sequence product. In the case of intracellular protective sequence products, such an assessment is done, preferably, using cell lysates or extracts. Such analysis will allow for a determination of the number of transformed cells necessary to achieve therapeutic efficacy *in vivo*, as well as optimization of the gene replacement protocol.

The tissue or cell type to be analyzed generally will include those that are known, or suspected, to express the protective sequence. The protein isolation methods employed herein may, for example, be such as those described in Harlow and Lane (1988, "Antibodies: A Laboratory Manual", Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York). The isolated cells can be derived from cell culture or from a patient. The analysis of cells taken from culture may be a necessary step in the assessment of cells to

be used as part of a cell-based gene therapy technique or, alternatively, to test the effect of compounds on the expression of the protective sequence.

Preferred diagnostic methods for the detection of protective sequence products, conserved variants or peptide fragments thereof, may involve, for example, immunoassays wherein the protective sequence products or conserved variants or peptide fragments are detected by their interaction with an anti-protective sequence product-specific antibody.

For example, antibodies, or fragments of antibodies, such as those described, above, in Section 5.3, may be used to, quantitatively or qualitatively, detect the presence of protective sequence products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody (see below, this Section) coupled with light microscopic, flow cytometric or fluorimetric detection. Such techniques are especially preferred for protective sequence products that are expressed on the cell surface.

The antibodies (or fragments thereof) useful in the present invention may, additionally, be employed histologically, as in immunofluorescence or immunoelectron microscopy, for *in situ* detection of protective sequence products, conserved variants or peptide fragments thereof. *In situ* detection may be accomplished by removing a histological specimen from a patient, and applying thereto a labeled antibody which binds to a protective sequence polypeptide. The antibody (or fragment) is preferably applied by overlaying the labeled antibody (or fragment) onto a biological sample. Through the use of such a procedure, it is possible to determine not only the presence of the protective sequence product, conserved variants or peptide fragments, but also its distribution in the examined tissue. Using the present invention, those of ordinary skill will readily recognize that any of a wide variety of histological methods (such as staining procedures) can be modified in order to achieve *in situ* detection of a protective sequence product.

Immunoassays for protective sequence products, conserved variants or peptide fragments thereof will typically comprise incubating a sample, such as a biological fluid, a tissue extract, freshly harvested cells or lysates of cells in the presence of a detectably labeled antibody capable of identifying the protective sequence product, conserved variants or peptide

fragments thereof, and detecting the bound antibody by any of a number of techniques well-known in the art.

The biological sample may be brought in contact with and immobilized onto a solid phase support or carrier, such as nitrocellulose, which is capable of immobilizing cells, cell particles or soluble proteins. The support may then be washed with suitable buffers followed by treatment with the detectably labeled protective sequence product specific antibody. The solid phase support may then be washed with the buffer a second time to remove unbound antibody. The amount of bound label on the solid support may then be detected by conventional means.

By "solid phase support or carrier" is intended any support capable of binding an antigen or an antibody. Well-known supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite. The nature of the carrier can be either soluble to some extent or insoluble for the purposes of the present invention. The support material may have virtually any possible structural configuration so long as the coupled molecule is capable of binding to an antigen or antibody. Thus, the support configuration may be spherical, as in a bead, or cylindrical, as in the inside surface of a test tube, or the external surface of a rod. Alternatively, the surface may be flat such as a sheet, test strip, etc. Preferred supports include polystyrene beads. Those skilled in the art will know many other suitable carriers for binding antibody or antigen, or will be able to ascertain the same by use of routine experimentation.

One of the ways in which the protective sequence product-specific antibody can be detectably labeled is by linking the same to an enzyme, such as for use in an enzyme immunoassay (EIA) (Voller, A., "The Enzyme Linked Immunosorbent Assay (ELISA)", 1978, Diagnostic Horizons 2:1-7, Microbiological Associates Quarterly Publication, Walkersville, MD); Voller, A. *et al.*, 1978, *J. Clin. Pathol.* 31:507-520; Butler, J.E., 1981, *Meth. Enzymol.* 73:482-523; Maggio, E. (ed.), 1980, Enzyme Immunoassay, CRC Press, Boca Raton, FL.; Ishikawa, E. *et al.*, (eds.), 1981, Enzyme Immunoassay, Kigaku Shoin, Tokyo). The enzyme that is bound to the antibody will react with an appropriate substrate, preferably a chromogenic substrate, in such a manner as to produce a chemical moiety which can be detected, for example, by spectrophotometric, fluorimetric or by visual means.

Enzymes which can be used to detectably label the antibody include, but are not limited to, malate dehydrogenase, staphylococcal nuclease, delta-5-steroid isomerase, yeast alcohol dehydrogenase, α -glycerophosphate dehydrogenase, triose phosphate isomerase, horseradish peroxidase, alkaline phosphatase, asparaginase, glucose oxidase,

5 b-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase, glucoamylase and acetylcholinesterase. The detection can be accomplished by colorimetric methods that employ a chromogenic substrate for the enzyme. Detection also may be accomplished by visual comparison of the extent of enzymatic reaction of a substrate in comparison with similarly prepared standards.

10 Detection may be accomplished also using any of a variety of other immunoassays. For example, by radioactively labeling the antibodies or antibody fragments, it is possible to detect protective sequence products through the use of a radioimmunoassay (RIA) (*see*, for example, Weintraub, B., Principles of Radioimmunoassays, Seventh Training Course on Radioligand Assay Techniques, The Endocrine Society, March, 1986). The
15 radioactive isotope can be detected by such means as the use of a gamma counter or a scintillation counter or by autoradiography.

It is also possible to label the antibody with a fluorescent compound. When the fluorescently labeled antibody is exposed to light of the proper wavelength, its presence can then be detected due to fluorescence. Among the most commonly used fluorescent
20 labeling compounds are fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, *o*-phthaldehyde and fluorescamine.

The antibody can also be detectably labeled using fluorescence emitting metals such as ^{152}Eu , or others of the lanthanide series. These metals can be attached to the antibody using such metal chelating groups as diethylenetriaminepentacetic acid (DTPA) or
25 ethylenediaminetetraacetic acid (EDTA).

The antibody also can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the chemiluminescent-tagged antibody is then determined by detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of particularly useful chemiluminescent labeling compounds
30 are luminol, isoluminol, thionin, acridinium ester, imidazole, acridinium salt and oxalate ester.

Likewise, a bioluminescent compound may be used to label the antibody of the present invention. Bioluminescence is a type of chemiluminescence found in biological systems in which a catalytic protein increases the efficiency of the chemiluminescent reaction. The presence of a bioluminescent protein is determined by detecting the presence of luminescence. Important bioluminescent compounds for purposes of labeling are luciferin, luciferase and aequorin.

5.4.2 Screening Assays for Compounds which Interact with Protective Sequence Products or Modulate Protective Sequence Activity

The following assays are designed to identify compounds which bind to a protective sequence product, compounds which bind to proteins, or portions of proteins which interact with a protective sequence product, compounds which modulate, *e.g.*, interfere with, the interaction of a protective sequence product with proteins and compounds which modulate the activity of the protective sequence (*i.e.*, modulate the level of protective sequence expression and/or modulate the level of protective sequence product activity). Assays may additionally be utilized which identify compounds which bind to protective sequence regulatory sequences (*e.g.*, promoter sequences; see *e.g.*, Platt, 1994, J. Biol. Chem. 269, 28558-28562), and which can modulate the level of protective sequence expression. Such compounds may include, but are not limited to, small organic molecules, such as ones which are able to cross the blood-brain barrier, gain to and/or entry into an appropriate cell and affect expression of the protective sequence or some other gene involved in a protective sequence regulatory pathway.

Methods for the identification of such proteins are described, below, in Section 5.4.2.2. Such proteins may be involved in the control and/or regulation of functions related to cell death. Further, among these compounds are compounds which affect the level of protective sequence expression and/or protective sequence product activity and which can be used in the therapeutic treatment of conditions, disorders, or diseases involving cell death as described, below, in Section 5.4.2.3.

Compounds may include, but are not limited to, peptides such as, for example, soluble peptides, including but not limited to, Ig-tailed fusion peptides, and members of random peptide libraries; (see, *e.g.*, Lam, *et al.*, 1991, *Nature* 354:82-84; Houghten, *et al.*,

1991, *Nature* 354:84-86), and combinatorial chemistry-derived molecular library made of D- and/or L-configuration amino acids, phosphopeptides (including, but not limited to members of random or partially degenerate, directed phosphopeptide libraries; see, *e.g.*, Songyang, *et al.*, 1993, *Cell* 72:767-778), antibodies (including, but not limited to, polyclonal, monoclonal, humanized, anti-idiotypic, chimeric or single chain antibodies, and FAb, F(ab')₂ and FAb expression library fragments, and epitope-binding fragments thereof), and small organic or inorganic molecules.

Such compounds may further comprise compounds, in particular drugs or members of classes or families of drugs, known to ameliorate the symptoms of a condition, disorder, or disease involving cell death.

Such compounds include families of antidepressants such as lithium salts, carbamazepine, valproic acid, lysergic acid diethylamide (LSD), *p*-chlorophenylalanine, *p*-propylidopacetamide dithiocarbamate derivatives *e.g.*, FLA 63; anti-anxiety drugs, *e.g.*, diazepam; monoamine oxidase (MAO) inhibitors, *e.g.*, iproniazid, clorgyline, phenelzine and isocarboxazid; biogenic amine uptake blockers, *e.g.*, tricyclic antidepressants such as desipramine, imipramine and amitriptyline; serotonin reuptake inhibitors *e.g.*, fluoxetine; antipsychotic drugs such as phenothiazine derivatives (*e.g.*, chlorpromazine (thorazine) and trifluopromazine)), butyrophenones (*e.g.*, haloperidol (Haldol)), thioxanthene derivatives (*e.g.*, chlorprothixene), and dibenzodiazepines (*e.g.*, clozapine); benzodiazepines; dopaminergic agonists and antagonists *e.g.*, L-DOPA, cocaine, amphetamine, α -methyl-tyrosine, reserpine, tetrabenazine, benzotropine, pargyline; noradrenergic agonists and antagonists *e.g.*, clonidine, phenoxybenzamine, phentolamine, tropolone.

Compounds identified via assays such as those described herein may be useful, for example, in elaborating the biological function of protective sequence products and for ameliorating conditions, disorders, or diseases involving cell death. Assays for testing the effectiveness of compounds identified by, for example, techniques such as those described in Sections 5.4.2.1 - 5.4.2.3, are discussed, below, in Section 5.4.2.4.

5.4.2.1 In Vitro Screening Assays for Compounds which Bind to Protective Sequence Products

5 *In vitro* systems may be designed to identify compounds capable of binding the protective sequence products of the invention. Compounds identified may be useful, for example, in modulating the activity of unimpaired and/or mutant protective sequence products, may be useful in elaborating the biological function of the protective sequence product, may be utilized in screens for identifying compounds which disrupt normal
10 protective sequence product interactions or may in themselves disrupt such interactions.

 The principle of the assays used to identify compounds which bind to the protective sequence product involves preparing a reaction mixture of the protective sequence product and the test compound under conditions and for a time sufficient to allow the two components to interact and bind, thus forming a complex which can be removed and/or
15 detected in the reaction mixture. These assays can be conducted in a variety of ways. For example, one method to conduct such an assay involves anchoring a protective sequence product or a test substance onto a solid support and detecting protective sequence product/test compound complexes formed on the solid support at the end of the reaction. In one embodiment of such a method, the protective sequence product may be anchored onto a solid
20 support, and the test compound, which is not anchored, may be labeled, either directly or indirectly.

 In practice, microtiter plates are conveniently utilized as the solid support. The anchored component may be immobilized by non-covalent or covalent attachments. Non-covalent attachment may be accomplished by simply coating the solid surface with a
25 solution of the protein and drying. Alternatively, an immobilized antibody, preferably a monoclonal antibody, specific for the protein to be immobilized may be used to anchor the protein to the solid surface. The surfaces may be prepared in advance and stored.

 In order to conduct the assay, the non-immobilized component is added to the coated surface containing the anchored component. After the reaction is complete, unreacted
30 components are removed (*e.g.*, by washing) under conditions such that any complexes formed will remain immobilized on the solid surface. The detection of complexes anchored on the solid surface can be accomplished in a number of ways. Where the previously non-

immobilized component is pre-labeled, the detection of label immobilized on the surface indicates that complexes were formed. Where the previously non-immobilized component is not pre-labeled, an indirect label can be used to detect complexes anchored on the surface; *e.g.*, using a labeled antibody specific for the previously non-immobilized component (the antibody, in turn, may be directly labeled or indirectly labeled with a labeled anti-Ig antibody).

Alternatively, a reaction can be conducted in a liquid phase, the reaction products separated from unreacted components, and complexes detected; *e.g.*, using an immobilized antibody specific for the protective sequence product or the test compound to anchor any complexes formed in solution, and a labeled antibody specific for the other component of the possible complex to detect anchored complexes.

5.4.2.2 Assays for Proteins which Interact with Protective Sequence Products

Any method suitable for detecting protein-protein interactions may be employed for identifying protective sequence product-protein interactions.

Among the traditional methods that may be employed are co-immunoprecipitation, cross-linking and co-purification through gradients or chromatographic columns. Utilizing procedures such as these allows for the identification of proteins, including intracellular proteins, which interact with protective sequence products. Once isolated, such a protein can be identified and can be used in conjunction with standard techniques, to identify proteins it interacts with. For example, at least a portion of the amino acid sequence of a protein which interacts with the protective sequence product can be ascertained using techniques well known to those of skill in the art, such as via the Edman degradation technique (see, *e.g.*, Creighton, 1983, "Proteins: Structures and Molecular Principles," W.H. Freeman & Co., N.Y., pp.34-49). The amino acid sequence obtained may be used as a guide for the generation of oligonucleotide mixtures that can be used to screen for gene sequences encoding such proteins. Screening may be accomplished, for example, by standard hybridization or PCR techniques. Techniques for the generation of oligonucleotide mixtures and the screening are well known. (See, *e.g.*, Ausubel, *supra*, and 1990, "PCR

Protocols: A Guide to Methods and Applications," Innis, *et al.*, eds. Academic Press, Inc., New York).

Additionally, methods may be employed which result in the simultaneous identification of genes that encode a protein that interacts with a protective sequence product.

5 These methods include, for example, probing expression libraries with labeled protective sequence product, using the protective sequence product in a manner similar to the well-known technique of antibody probing of lgt11 libraries.

One method that detects protein interactions *in vivo*, the two-hybrid system, is described in detail for illustration only and not by way of limitation. One version of this
10 system has been described (Chien, *et al.*, 1991, *Proc. Natl. Acad. Sci. USA*, 88:9578-9582) and is commercially available from Clontech (Palo Alto, CA).

Briefly, utilizing such a system, plasmids are constructed which encode two hybrid proteins: one consists of the DNA-binding domain of a transcription activator protein fused to the protective sequence product and the other consists of the transcription activator
15 protein's activation domain fused to an unknown protein which is encoded by a cDNA which has been recombined into this plasmid as part of a cDNA library. The DNA-binding domain fusion plasmid and the cDNA library are transformed into a strain of the yeast *Saccharomyces cerevisiae* that contains a reporter gene (*e.g.*, HBS or *lacZ*) whose regulatory region contains the transcription activator's binding site. Either hybrid protein alone cannot activate
20 transcription of the reporter gene: the DNA-binding domain hybrid cannot because it does not provide activation function and the activation domain hybrid cannot because it cannot localize to the activator's binding sites. Interaction of the two hybrid proteins reconstitutes the functional activator protein and results in expression of the reporter gene, which is detected by an assay for the reporter gene product.

25 The two-hybrid system or related methodologies may be used to screen activation domain libraries for proteins that interact with the "bait" gene product. By way of example, and not by way of limitation, protective sequence products of the invention may be used as the bait gene product. Total genomic or cDNA sequences are fused to the DNA encoding an activation domain. This library and a plasmid encoding a hybrid of a bait
30 protective sequence product fused to the DNA-binding domain are co-transformed into a yeast reporter strain, and the resulting transformants are screened for those which express the

reporter gene. For example, a bait protective sequence, such as the open reading frame of the gene, can be cloned into a vector such that it is translationally fused to the DNA encoding the DNA-binding domain of the GAL4 protein. These colonies are purified and the library plasmids responsible for reporter gene expression are isolated. DNA sequencing is then used to identify the proteins encoded by the library plasmids.

A cDNA library of the cell line, from which proteins which interact with bait protective sequence products are to be detected, can be made using methods routinely practiced in the art. According to the particular system described herein, for example, the cDNA fragments can be inserted into a vector such that they are translationally fused to the transcriptional activation domain of GAL4. Such a library can be co-transformed along with the bait protective sequence-GAL4 fusion plasmid into a yeast strain that contains a lacZ gene driven by a promoter that contains GAL4 activation sequence. A cDNA encoded protein, fused to a GAL4 transcriptional activation domain that interacts with bait protective sequence product will reconstitute an active GAL4 protein and thereby drive expression of the HIS3 gene. Colonies that express HIS3 can be detected by their growth on petri dishes containing semi-solid agar based media lacking histidine. The cDNA can then be purified from these strains, and used to produce and isolate the bait protective sequence product-interacting protein using techniques routinely practiced in the art.

5.4.2.3 Assays for Compounds which Interfere with or Potentiate Protective Sequence Products Macromolecule Interaction

The protective sequence products may, *in vivo*, interact with one or more macromolecules, including intracellular macromolecules, such as proteins. Such macromolecules may include, but are not limited to, nucleic acid molecules and those proteins identified via methods such as those described, above, in Sections 5.4.2.1 - 5.4.2.2. For purposes of this discussion, the macromolecules are referred to herein as "binding partners". Compounds that disrupt protective sequence product binding to a binding partner may be useful in regulating the activity of the protective sequence product, especially mutant protective sequence products. Such compounds may include, but are not limited to molecules such as peptides, and the like, as described, for example, in Section 5.4.2.1 above.

The basic principle of an assay system used to identify compounds which interfere with or potentiate the interaction between the protective sequence product and a binding partner or partners involves preparing a reaction mixture containing the protective sequence product and the binding partner under conditions and for a time sufficient to allow the two to interact and bind, thus forming a complex. In order to test a compound for inhibitory activity, the reaction mixture is prepared in the presence and absence of the test compound. The test compound may be initially included in the reaction mixture, or may be added at a time subsequent to the addition of protective sequence product and its binding partner. Control reaction mixtures are incubated without the test compound or with a compound that is known not to block complex formation. The formation of any complexes between the protective sequence product and the binding partner is then detected. The formation of a complex in the control reaction, but not in the reaction mixture containing the test compound, indicates that the compound interferes with the interaction of the protective sequence product and the binding partner. Additionally, complex formation within reaction mixtures containing the test compound and normal protective sequence product also may be compared to complex formation within reaction mixtures containing the test compound and a mutant protective sequence product. This comparison may be important in those cases wherein it is desirable to identify compounds that disrupt interactions of mutant but not normal protective sequence product.

In order to test a compound for potentiating activity, the reaction mixture is prepared in the presence and absence of the test compound. The test compound may be initially included in the reaction mixture, or may be added at a time subsequent to the addition of protective sequence product and its binding partner. Control reaction mixtures are incubated without the test compound or with a compound that is known not to block complex formation. The formation of any complexes between the protective sequence product and the binding partner is then detected. Increased formation of a complex in the reaction mixture containing the test compound, but not in the control reaction, indicates that the compound enhances and therefore potentiates the interaction of the protective sequence product and the binding partner. Additionally, complex formation within reaction mixtures containing the test compound and normal protective sequence product may also be compared to complex formation within reaction mixtures containing the test compound and a mutant protective

sequence product. This comparison may be important in those cases wherein it is desirable to identify compounds that enhance interactions of mutant but not normal protective sequence product.

5 In alternative embodiments, the above assays may be performed using a reaction mixture containing the protective sequence product, a binding partner and a third compound which disrupts or enhances protective sequence product binding to the binding partner. The reaction mixture is prepared and incubated in the presence and absence of the test compound, as described above, and the formation of any complexes between the
10 protective sequence product and the binding partner is detected. In this embodiment, the formation of a complex in the reaction mixture containing the test compound, but not in the control reaction, indicates that the test compound interferes with the ability of the second compound to disrupt protective sequence product binding to its binding partner.

The assays for compounds that interfere with or potentiate the interaction of
15 the protective sequence products and binding partners can be conducted in a heterogeneous or homogeneous format. Heterogeneous assays involve anchoring either the protective sequence product or the binding partner onto a solid support and detecting complexes formed on the solid support at the end of the reaction. In homogeneous assays, the entire reaction is carried out in a liquid phase. In either approach, the order of addition of reactants can be varied to
20 obtain different information about the compounds being tested. For example, test compounds which interfere with or potentiate the interaction between the protective sequence products and the binding partners, *e.g.*, by competition, can be identified by conducting the reaction in the presence of the test substance; *i.e.*, by adding the test substance to the reaction mixture prior to or simultaneously with the protective sequence product and interactive intracellular
25 binding partner. Alternatively, test compounds which disrupt preformed complexes, *e.g.*, compounds with higher binding constants which displace one of the components from the complex, can be tested by adding the test compound to the reaction mixture after complexes have been formed. The various formats are described briefly below.

In a heterogeneous assay system, either the protective sequence product or the
30 interactive binding partner, is anchored onto a solid surface, while the non-anchored species is labeled, either directly or indirectly. In practice, microtiter plates are conveniently utilized.

background. In this way, test substances that disrupt protective sequence product/binding partner interaction can be identified.

5 In another embodiment of the invention, these same techniques can be employed using peptide fragments which correspond to the binding domains of the protective sequence product and/or the binding partner (in cases where the binding partner is a protein), in place of one or both of the full length proteins. Any number of methods routinely practiced in the art can be used to identify and isolate the binding sites. These methods include, but are not limited to, mutagenesis of the gene encoding one of the proteins and screening for disruption of binding in a co-immunoprecipitation assay. Compensating
10 mutations in the gene encoding the second species in the complex can then be selected. Sequence analysis of the genes encoding the respective proteins will reveal the mutations that correspond to the region of the protein involved in interactive binding. Alternatively, one protein can be anchored to a solid surface using methods described in this Section above, and allowed to interact with and bind to its labeled binding partner, which has been treated with a
15 proteolytic enzyme, such as trypsin. After washing, a short, labeled peptide comprising the binding domain may remain associated with the solid material, which can be isolated and identified by amino acid sequencing. Also, once the gene coding for the segments is engineered to express peptide fragments of the protein, it can then be tested for binding activity and purified or synthesized.

20 For example, and not by way of limitation, a protective sequence product can be anchored to a solid material as described, above, in this Section by making a GST-1 fusion protein and allowing it to bind to glutathione agarose beads. The binding partner can be labeled with a radioactive isotope, such as ^{35}S , and cleaved with a proteolytic enzyme such as trypsin. Cleavage products can then be added to the anchored GST-1 fusion protein and
25 allowed to bind. After washing away unbound peptides, labeled bound material, representing the binding partner binding domain, can be eluted, purified and analyzed for amino acid sequence by well-known methods. Peptides so identified can be produced synthetically or produced using recombinant DNA technology.

5.4.2.4 Assays for the Identification of Compounds which Modulate Conditions, Disorders, or Diseases Involving Cell Death

5 Compounds, including, but not limited to, binding compounds identified via assay techniques such as those described, above, in Sections 5.4.2.1 - 5.4.2.3, can be tested for the ability to ameliorate symptoms of a condition, disorder, or disease involving cell death.

10 It should be noted that the assays described herein can be used to identify compounds which affect activity by either affecting protective sequence expression or by affecting the level of protective sequence product activity. For example, compounds may be identified which are involved in another step in the pathway in which the protective sequence and/or protective sequence product is involved, such as, for example, a step which is either "upstream" or "downstream" of the step in the pathway mediated by the protective sequence.

15 Such compounds may, by affecting this same pathway, modulate the effect on the development of conditions, disorders, or diseases involving cell death. Such compounds can be used as part of a therapeutic method for the treatment of the condition, disorder, or disease.

20 Described below are cell-based and animal model-based assays for the identification of compounds exhibiting such an ability to ameliorate symptoms of a condition, disorder, or disease involving cell death.

 First, cell-based systems can be used to identify compounds which may act to ameliorate symptoms of a condition, disorder, or disease, including, but not limited to, those described in Section 5.4.1.1. Such cell systems can include, for example, recombinant or non-recombinant cell, such as cell lines, which express the protective sequence of interest.

25 In utilizing such cell systems, cells which express the protective sequence of interest may be exposed to a compound suspected of exhibiting an ability to ameliorate symptoms of a condition, disorder, or disease involving cell death at a sufficient concentration and for a sufficient time to elicit such an amelioration of such symptoms in the exposed cells. After exposure, the cells can be assayed to measure alterations in the expression of the protective sequence, *e.g.*, by assaying cell lysates for cerebral mRNA transcripts (*e.g.*, by Northern analysis) or for protective sequence products expressed by the cell; compounds which modulate expression of the protective sequence are good candidates

30

as therapeutics.

In addition, animal-based systems or models for a condition, disorder, or disease involving cell death, for example, transgenic mice containing a human or altered form of a protective sequence, may be used to identify compounds capable of ameliorating symptoms of the condition, disorder, or disease. Such animal models may be used as test substrates for the identification of drugs, pharmaceuticals, therapies and interventions. For example, animal models may be exposed to a compound suspected of exhibiting an ability to ameliorate symptoms, at a sufficient concentration and for a sufficient time to elicit such an amelioration of symptoms of a condition, disorder, or disease involving cell death. The response of the animals to the exposure may be monitored by assessing the reversal of the symptoms of the condition, disorder, or disease.

With regard to intervention, any treatments that reverse any aspect of symptoms of a condition, disorder, or disease involving cell death, should be considered as candidates for human therapeutic intervention in such conditions, disorders, or diseases. Dosages of test agents may be determined by deriving dose-response curves, as discussed in Section 5.5.1, below.

5.4.3 Additional Uses for the Protective Sequences, Protective Sequence Products, or Their Regulatory Elements

In addition to the uses described above, the polynucleotides of the present invention can be used for various other purposes. For example, they can be used to express recombinant protein for analysis, characterization or therapeutic use; as molecular weight markers on gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic conditions, disorders, or diseases; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response.

The proteins provided by the present invention can similarly be used to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E. F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S. L. and A. R. Kimmel eds., 1987.

5.5 Pharmaceutical Preparations and Methods of Administration

The compounds which are determined to affect protective sequence expression or gene product activity can be administered to a patient at therapeutically effective doses to treat or ameliorate a condition, disorder, or disease involving cell death or modulate a cell death-related process described herein. A therapeutically effective dose refers to that amount of the compound sufficient to result in amelioration of symptoms of such a condition, disorder, or disease.

5.5.1 Effective Dose

Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD₅₀/ED₅₀.

Compounds that exhibit large therapeutic indices are preferred. While compounds which exhibit toxic side effects may be used, care should be taken to design a delivery system which targets such compounds to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

5 The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the
10 invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range which includes the IC_{50} (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in
15 plasma may be measured, for example, by high performance liquid chromatography.

 As defined herein, a therapeutically effective amount of antibody, protein, or polypeptide (*i.e.*, an effective dosage) ranges from about 0.001 to 30 mg/kg body weight, preferably about 0.01 to 25 mg/kg body weight, more preferably about 0.1 to 20 mg/kg body weight, and even more preferably about 1 to 10 mg/kg, 2 to 9 mg/kg, 3 to 8 mg/kg, 4 to 7
20 mg/kg, or 5 to 6 mg/kg body weight.

 The skilled artisan will appreciate that certain factors may influence the dosage required to effectively treat a subject, including but not limited to the severity of the disease or condition, disorder, or disease, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically
25 effective amount of a protein, polypeptide, or antibody can include a single treatment or, preferably, can include a series of treatments. In a preferred example, a subject is treated with antibody, protein, or polypeptide in the range of between about 0.1 to 20 mg/kg body weight, one time per week for between about 1 to 10 weeks, preferably between 2 to 8 weeks, more preferably between about 3 to 7 weeks, and even more preferably for about 4, 5, or 6 weeks.
30 It will also be appreciated that the effective dosage of antibody, protein, or polypeptide used for treatment may increase or decrease over the course of a particular treatment. Changes in

dosage may result and become apparent from the results of diagnostic assays as described herein.

5.5.2 Formulations and Use

5 Pharmaceutical compositions for use in accordance with the present invention may be formulated in conventional manner using one or more physiologically acceptable carriers or excipients.

 Thus, the compounds and their physiologically acceptable salts and solvates may be formulated for administration by inhalation or insufflation (either through the mouth or the nose) or oral, buccal, parenteral rectal or topical administration.

 For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (*e.g.*, pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (*e.g.*, lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (*e.g.*, magnesium stearate, talc or silica); disintegrants (*e.g.*, potato starch or sodium starch glycolate); or wetting agents (*e.g.*, sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (*e.g.*, sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (*e.g.*, lecithin or acacia); non-aqueous vehicles (*e.g.*, almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (*e.g.*, methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavoring, coloring and sweetening agents as appropriate.

 Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

 For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of *e.g.*, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

In certain embodiments, it may be desirable to administer the pharmaceutical compositions of the invention locally to the area in need of treatment. This may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, *e.g.*, in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. In one embodiment, administration can be by direct injection at the site (or former site) of a malignant tumor or neoplastic or pre-neoplastic tissue.

For topical application, the compounds may be combined with a carrier so that an effective dosage is delivered, based on the desired activity.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection.

Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The compositions may, if desired, be presented in a pack or dispenser device that may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration.

6 EXAMPLE: SEQUENCE AND CHARACTERIZATION OF PROTECTIVE SEQUENCES

In the example presented herein, the sequence and characterization of the protective sequences are provided.

6.1 Materials and Methods

6.1.1 Preparation of DNA

A human fetal brain cDNA library (Gibco), in which individual clones were inserted into the NotI-SalI site of the pCMV-SPORT2 vector, was diluted 200,000 fold in LB broth (DIFCO Laboratories) containing 0.2 mg/ml ampicillin (Sigma). The diluted library (100-140 μ l) was then plated and grown on LB agar (DIFCO Laboratories) bioassay plates with 0.2 mg/ml ampicillin. Plates were incubated at 37°C for 24 hours. Single colonies were then used to inoculate deep-well blocks containing 1.5 ml LB broth containing 0.2 mg/ml ampicillin. Inoculated cultures were incubated at 37°C with agitation at 150-200 rpm for 18-24 hours. Replicate plates were created from the cultures by adding 20 μ l of culture to 80 μ l of LB broth containing 18% glycerol and 0.2 mg/ml ampicillin and stored at -80°C. Remaining bacterial cells were centrifuged at 1000 x g for 6 minutes to collect the cells at the bottom. Following centrifugation, the broth was decanted off of the bacterial pellet and the pellet resuspended and then stored in 100 μ l of Cell Resuspension Solution (Promega) at 4°C for up to one week.

Plasmid DNA was extracted using Promega MagneSil kits with a modified protocol. The pelleted bacteria were re-suspended and 50 μ l was transferred into a round bottom plate that rests on a magnet. Cell Lysis Solution (50 μ l) was added and the plate was incubated at room temperature without agitation for 30 seconds. Following lysis, 70 μ l of a Neutralization Solution/MagneSil Paramagnetic Particles mixture (pre-mixed at a ratio of

6:1) was added. The reaction was mixed by pipetting and incubated at room temperature without agitation for 5 minutes to allow the magnetic particles to be drawn to the magnet. The supernatant containing plasmid DNA was then transferred to a new plate and stored at -20°C.

5 Individual clones were chosen for their ability to delay or prevent cell death when introduced into a cell predisposed to undergoing cell death, relative to a corresponding cell into which no exogenous protective sequence had been introduced.

6.1.2 Sequence Characterization of the DNA

10 The cDNA inserts of the clonally pure plasmids which are selected for their ability to protect cells from cell death when introduced into cells predisposed to undergo cell death are sequenced using the ABI Big Dye terminator Cycle Sequencing Ready Reaction Kit and subsequently analyzed on the ABI310 capillary sequencing machine (PE Biosystems, Foster City, CA).

15 Briefly, 0.5 mg of plasmid DNA is mixed with 3.2 pmole of either the M13 forward (5'-TGTAACGACGGCCAGT-3'; SEQ ID NO:465) or the M13 reverse (5'-CAGGAAACAGCTATGACC-3'; SEQ ID NO:466) sequencing primer and 8 ml of the terminator ready reaction mix in a total volume of 20 ml. The cycle sequencing reaction is carried out in a thermocycler (PCR machine) using standard methods known by those skilled
20 in the art. The extension products from the sequencing reaction are purified by precipitation using isopropanol. 80 ml of 75% isopropanol is added to the sample and after thorough mixing, the sample is incubated at room temperature (25°C) for 20 minutes. The sample is then centrifuged at 12,000 x g for 20 minutes at room temperature. The supernatant is removed and the pellet is rinsed once by addition of 250 ml of 75% isopropanol followed by
25 centrifugation as above for 5 minutes. The supernatant is removed and the sample air-dried for 10 minutes. The sample is then resuspended in 20 ml of TSR (template suppression reagent) and denatured by heating at 94°C for 2 minutes and rapidly cooling on ice. The subsequent electrophoresis and analysis is carried out on the ABI310 sequencer according to the manufacturer's protocol. The entire cDNA clone is similarly sequenced by the use of
30 sequence specific internal primers as required.

6.1.3 Sequence Comparison

The sequence data for the protective cDNA clones is compared using the BLAST 2.0 algorithm (Altschul, SF *et al.*, 1997, Nuc. Acids Res. 25:3389) against known sequences in the GeneBank sequence database maintained by NCBI (National Center for
5 Biotechnology Information). This program uses the two-hit method to find homology within the database. The BLAST nucleotide searches are performed with the "BLAST N" program (wordlength = 11) to obtain nucleic acids homologous to nucleic acid molecules of the invention. BLAST protein searches of potential ORFs are performed with the "BLAST P"
10 program (wordlength = 3) to obtain amino acid sequences homologous to the ORFs of the invention.

6.1.4 Immuno-Cytochemistry Protocol for the Characterization of Protected Cells

Transfected tissue is immersed in freshly prepared 2.5% paraformaldehyde
15 (PFA) in phosphate buffered saline (PBS) for two hours to fix the tissue. PFA is removed by aspiration and the fixed tissue washed consecutively four times in PBS for 15 minutes, changing the PBS solution between each wash. Upon removal of the final PBS wash, the tissue is immersed in a blocking solution consisting of 10% goat serum, 2% bovine serum albumin (BSA), and 0.25% Triton X-100 for a duration of two hours.

20 After removal of the blocking solution, the tissue is immersed in a primary antibody solution, freshly prepared by adding rabbit anti-GFP polyclonal (1:2000 ul) into blocking solution, for an incubation period of twelve hours at 4°C.

After removal of the primary antibody solution, the tissue is washed consecutively four times in PBS for 10 minutes, changing the PBS solution between each
25 wash. An anti-rabbit, fluorescently conjugated secondary antibody, diluted in PBS at a concentration of 1:500, is then added to the tissue and allowed to incubate at room temperature for four hours. The secondary antibody solution is removed by aspiration and the tissue washed consecutively four times in PBS for 15 minutes, changing the PBS solution between each wash. After the final wash is removed, the tissue is mounted on glass slides
30 and dried at 37°C for thirty minutes. A three-minute xylene incubation is performed before the addition of coverslips to preserve the slices.

6.2 Results

The following protective sequences, which were obtained using the methods described in Section 6.1, were chosen based on their ability to prevent, delay, or rescue cells predisposed to undergo cell death, relative to a corresponding cell into which no exogenous protective sequence had been introduced.

6.2.1 Protective sequence CNI-00718

Protective sequence CNI-00718 (SEQ. ID NO:1) is a completely novel sequence which comprises 1794 nucleotides. Twenty-eight (28) potential ORFs have been identified within the protective sequence and are depicted in Table 2. The longest ORF is 112 amino acids. BLAST sequence comparison analysis of CNI-00718 against known nucleotide and protein sequences in the GenBank database reveals no significant homology at either the nucleotide or the amino acid level. As shown in Figure 3F, CNI-00718 caused about a 20-fold increase in the number of surviving neurons in stroked rat cortical brain slices compared to negative control slices which were exposed to EGFP with no protective sequence.

6.2.2 Protective sequence CNI-00722

Protective sequence CNI-00722 (SEQ. ID NO:58) comprises 810 nucleotides. Twelve (12) potential ORFs have been identified within the protective sequence and are depicted in Table 3. The longest ORF of the cDNA encodes 44 amino acids. BLAST sequence comparison analysis of CNI-00722 against known nucleic acids in the GenBank database reveals homology with the sequence encoding the human chromosome 16 BAC clone CIT987-SKA-113A6 (ACC. No. AC002299). At the nucleotide level, the overall percent homology between CNI-00722 and CIT987-SKA-113A6 is 99.6% (783/785 bases). CIT987-SKA-113A6 is an unidentified DNA. As shown in Figure 3F, CNI-00722 caused about a 21-fold increase in the number of surviving neurons in stroked rat cortical brain slices compared to negative control slices which were exposed to EGFP with no protective sequence.

6.2.3 Protective sequence CNI-00725

Protective sequence CNI-00725 (SEQ. ID NO:83) comprises 920 nucleotides.

Eleven (11) potential ORFs have been identified within the protective sequence and are depicted in Table 4. BLAST sequence comparison analysis of CNI-00725 against known nucleic acids in the GenBank database reveals a 97% identity (870/897 bases) with a human mitochondrial sequence encoding the 16S rRNA and tRNA for the amino acid Leucine (ACC. No. V00710). However, most of the homology (95%) is with the 16S rRNA sequence. As shown in Figure 3F, CNI-00725 caused about a 14-fold increase in the number of surviving neurons in stroked rat cortical brain slices compared to negative control slices which were exposed to EGFP with no protective sequence.

6.2.4 Protective sequence CNI-00726

Protective sequence CNI-00726 (SEQ. ID NO:106) comprises 2144

nucleotides. Twenty-six (26) potential ORFs have been identified within the protective sequence and are depicted in Table 5. The longest ORF of CNI-00726 encodes 147 amino acids. BLAST sequence comparison analysis of CNI-00726 against known nucleic acids in the GenBank database reveals a 99.7% identity (1820/1825 bases) with the human ubiquitin-conjugating enzyme variant 1, UBE2V1 (ACC No. NM_003349); a 99.6% identity (1820/1826 bases) with the human DNA-binding protein CROC-1A (ACC No. U39360); and a 72.5% identity (401/553 bases) with the human MMS2 protein (ACC No. AF049140). At the protein level, CNI-00726 has a 100% identity with the 80-221 amino acid region of UBE2VI; a 97% identity (136/140 amino acids) with the 31-170 amino acid region of CROC-1A; and a 90% identity (132/147 amino acids) with the human MMS2 protein. The enzyme UBE2V1 may be involved in controlling differentiation by affecting the distribution of cells in different phases during the cell cycle (Sancho, *et al.* 1998, *Mol. Cell. Biol.* 18: 576-89). The protein CROC-1A is capable of transcriptionally activating the FOS promoter (Rothofsky & Lin, 1997, *Gene* 195: 141-9; Lin & Rothofsky, U.S. Patent No. 5,736,331). As shown in Figure 3F, CNI-00726 caused about a 19-fold increase in the number of surviving neurons in stroked rat cortical brain slices compared to negative control slices which were exposed to EGFP with no protective sequence.

6.2.5 Protective sequence CNI-00727

Protective sequence CNI-00727 (SEQ. ID NO:159) is a completely novel sequence which comprises 1293 nucleotides. Nineteen (19) potential ORFs have been identified within the protective sequence and are depicted in Table 6. The longest ORF is 54 amino acids. BLAST sequence comparison analysis of CNI-00727 against known nucleotide and protein sequences in the GenBank database reveals no significant homology at either the nucleotide or the amino acid level. As shown in Figure 3F, CNI-00727 caused about a 17-fold increase in the number of surviving neurons in stroked rat cortical brain slices compared to negative control slices which were exposed to EGFP with no protective sequence.

6.2.6 Protective sequence CNI-00728

Protective sequence CNI-00728 (SEQ. ID NO:198) comprises 1466 nucleotides. Twenty-four (24) potential ORFs have been identified within the protective sequence and are depicted in Table 7. The longest ORF is 59 amino acids. BLAST sequence comparison analysis of CNI-00728 against known nucleic acids in the GenBank database reveals a 99.9% identity (1342/1343 bases) with the 3' untranslated region of human sorting nexin 10 mRNA (ACC. No. AF121860). As shown in Figure 3F, CNI-00728 caused about a 10-fold increase in the number of surviving neurons in stroked rat cortical brain slices compared to negative control slices which were exposed to EGFP with no protective sequence.

6.2.7 Protective sequence CNI-00729

Protective sequence CNI-00729 (SEQ. ID NO:247) comprises 1659 nucleotides. Twenty-two (22) potential ORFs have been identified within the protective sequence and are depicted in Table 8. BLAST sequence comparison analysis of CNI-00729 against known nucleic acids in the GenBank database reveals a 99.9% identity (1611/1612 bases) with a human actin binding protein, p57 (ACC No. D44497); a 99.9% identity (1561/1562 bp) with human coronin (ACC No. X89109); and a 99.7% identity (1585/1589 bp) with human coronin-like protein, HCORO1 (ACC No. U34690). At the amino acid level, CNI-00729 is identical to human actin protein, p57; identical to human coronin; and 99% identical (459/461 aa) with human coronin-like protein (Suzuki, Jpn. Kokai Tokyo Koho Patent No. 96119996). The p57 protein is an actin-binding protein and a member of the

coronin family of proteins. The coronins are proteins involved in cell locomotion, cytokinesis, and actin-mediated cellular processes such as phagocytosis (deHostos, 1999, *Trends Cell Biol.* 9: 345-50). As shown in Figure 3F, CNI-00729 caused about a 13-fold increase in the number of surviving neurons in stroked rat cortical brain slices compared to negative control slices which were exposed to EGFP with no protective sequence.

6.2.8 Protective sequence CNI-00730

Protective sequence CNI-00730 (SEQ. ID NO:292) comprises 722 nucleotides. Nine (9) potential ORFs have been identified within the protective sequence and are depicted in Table 9. The longest ORF of the cDNA encodes 142 amino acids. BLAST sequence comparison analysis of CNI-00730 against known nucleic acids in the GenBank database reveals homology with the sequence encoding human mitochondrial ATP synthase, F0 complex, subunit 9 (ACC. No. NM_001689). At the nucleotide level, the overall percent homology between CNI-00730 and human mitochondrial ATP synthase, F0 complex, subunit 9 is 99.4% (651/655 bp). At the amino acid level, the CNI-00730 and human mitochondrial ATP synthase, F0 complex, subunit 9 proteins are identical. There are three reported genes (P1, P2, and P3) that encode identical forms of mature human mitochondrial ATP synthase, F0 complex, subunit 9; CNI-00730 is homologous to the P3 gene (Yan, *et al.* 1994, *Genomics* 24: 375-7). Subunit 9 accumulates in the lysosomes of individuals affected with the juvenile and late-infantile forms of neuronal ceroid lipofuscinosis (Batten disease) (Tanner, *et al.*, 1997, *Biochim. Biophys. Acta* 1361: 251-62). As shown in Figure 3F, CNI-00730 caused about a 14-fold increase in the number of surviving neurons in stroked rat cortical brain slices compared to negative control slices which were exposed to EGFP with no protective sequence.

6.2.9 Protective sequence CNI-00731

Protective sequence CNI-00731 (SEQ. ID NO:311) comprises 364 nucleotides. Seven (7) potential ORFs have been identified within the protective sequence and are depicted in Table 10. The longest ORF is 32 amino acids. BLAST sequence comparison analysis of CNI-00731 against known nucleic acids in the GenBank database reveals a 98.5% identity (322/326 bases) with the 3' untranslated region of human interferon-

induced cellular resistance mediator protein (MxA) mRNA (ACC. No. M30817). As shown in Figure 3F, CNI-00731 caused about an 11-fold increase in the number of surviving neurons in stroked rat cortical brain slices compared to negative control slices which were exposed to EGFP with no protective sequence.

5

6.2.10 Protective sequence CNI-00732

Protective sequence CNI-00732 (SEQ. ID NO:326) comprises 1046 nucleotides. Eight (8) potential ORFs have been identified within the protective sequence and are depicted in Table 11. The longest ORF is 50 amino acids. BLAST sequence comparison analysis of CNI-00732 against known nucleic acids in the GenBank database reveals a 94% identity (949/1013 bases) with a human mitochondrial sequence encoding the 12S rRNA and tRNA for the amino acid Valine (ACC. No. V00710). However, most of the homology (97%) is with the 12S rRNA sequence. As shown in Figure 3F, CNI-00732 caused about a 12-fold increase in the number of surviving neurons in stroked rat cortical brain slices compared to negative control slices which were exposed to EGFP with no protective sequence.

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7 DEPOSIT OF DNA

The following DNA clones were deposited with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209, under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure, and comply with the criteria set forth in 37 C.F.R. § 1.801-1.809 regarding availability and permanency of deposits. The deposits were made on the date indicated and assigned the indicated accession number:

20

25

<u>Microorganism Deposit</u>	<u>ATCC Deposit No.</u>	<u>Date of Deposit</u>
CNI-NPP2-CP10	PTA-1492	March 16, 2000

30

CNI-NPP2-CP10 represents a composite deposit of a mixture of ten (10) DNA clones. To distinguish and isolate each of the individual DNA, a sample of the DNA preparation can be digested with *Not I* and *Sal I*, and the resulting products can be separated

by standard gel electrophoresis techniques using a 1% agarose gel in TAE buffer. Liberated inserts are of the following approximate sizes:

	1:	CNI-00718	1794 bp
	2:	CNI-00722	810 bp
5	3:	CNI-00725	920 bp
	4:	CNI-00726	2144 bp
	5:	CNI-00727	1293 bp
	6:	CNI-00728	1466 bp
	7:	CNI-00729	1659 bp
10	8:	CNI-00730	722 bp
	9:	CNI-00731	364 bp
	10:	CNI-00732	1046 bp

8 REFERENCES CITED

15 The present invention is not to be limited in scope by the specific embodiments described herein, which are intended as single illustrations of individual aspects of the invention, and functionally equivalent methods and components are within the scope of the invention. Indeed, various modifications of the invention, in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing
20 description and accompanying drawings.

All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be
25 incorporated by reference.

WHAT IS CLAIMED IS:

1. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes a polypeptide comprising:
 - 5 (a) an amino acid sequence shown in Figures 4(A-AB);
 - (b) an amino acid sequence shown in Figures 5(A-L);
 - (c) an amino acid sequence shown in Figures 6(A-K);
 - (d) an amino acid sequence shown in Figures 7(A-Z);
 - (e) an amino acid sequence shown in Figures 8(A-S);
 - 10 (f) an amino acid sequence shown in Figures 9(A-X);
 - (g) an amino acid sequence shown in Figures 10(A-V);
 - (h) an amino acid sequence shown in Figures 11(A-I);
 - (i) an amino acid sequence shown in Figures 12(A-G); or
 - (j) the amino acid sequence shown in Figure 13(A-H).
- 15 2. An isolated nucleic acid molecule comprising:
 - (a) a nucleic acid sequence shown in Figures 4(A-AB);
 - (b) a nucleic acid sequence shown in Figures 5(A-L);
 - (c) a nucleic acid sequence shown in Figures 6(A-K);
 - 20 (d) a nucleic acid sequence shown in Figures 7(A-Z);
 - (e) a nucleic acid sequence shown in Figures 8(A-S);
 - (f) a nucleic acid sequence shown in Figures 9(A-X);
 - (g) a nucleic acid sequence shown in Figures 10(A-V);
 - (h) a nucleic acid sequence shown in Figures 11(A-I);
 - 25 (i) a nucleic acid sequence shown in Figures 12(A-G);
 - (j) a nucleic acid sequence shown in Figure 13 (A-H); or
 - (k) a nucleic acid sequence shown in Figures 1(A-J).
3. An isolated nucleic acid molecule comprising a complement of the nucleic acid molecule of any one of Claims 1 and 2.
- 30

4. An isolated nucleic acid molecule which hybridizes to the nucleic acid molecule of Claim 3 under highly stringent conditions.

5. An isolated nucleic acid molecule which hybridizes to the nucleic acid molecule of Claim 3 under moderately stringent conditions.

6. The isolated nucleic acid molecule of Claim 4, wherein said isolated nucleic acid molecule encodes a protective sequence product.

7. The isolated nucleic acid molecule of Claim 5, wherein said isolated nucleic acid molecule encodes a protective sequence product.

8. A vector comprising the nucleic acid of any one of Claims 1 and 2.

9. The vector of claim 8, wherein said vector is a viral vector.

10. An expression vector comprising the nucleic acid of any one of Claims 1 and 2 operatively associated with a regulatory nucleic acid controlling the expression of the nucleic acid in a host cell.

11. A host cell genetically engineered to contain the nucleic acid of any one of Claims 1 and 2.

12. A host cell genetically engineered to express the nucleic acid of any one of Claims 1 and 2 operatively associated with a regulatory nucleic acid controlling expression of the nucleic acid in said host cell.

13. The host cell of Claim 12, wherein said host cell is a neuronal cell.

14. The host cell of Claim 13, wherein said neuronal cell is a PC-12 cell or a primary dissociated neuron.

15. A transgenic, non-human animal which has been genetically engineered to contain a transgene comprising the nucleic acid of any one of Claims 1 and 2.

5 16. The transgenic, non-human animal of Claim 15, wherein the transgene is expressed.

17. An isolated polypeptide comprising:

- 10 (a) an amino acid sequence shown in Figures 4(A-AB);
(b) an amino acid sequence shown in Figures 5(A-L);
(c) an amino acid sequence shown in Figures 6(A-K);
(d) an amino acid sequence shown in Figures 7(A-Z);
(e) an amino acid sequence shown in Figures 8(A-S);
(f) an amino acid sequence shown in Figures 9(A-X);
(g) an amino acid sequence shown in Figures 10(A-V);
15 (h) an amino acid sequence shown in Figures 11(A-I);
(i) an amino acid sequence shown in Figures 12(A-G); or
(j) the amino acid sequence shown in Figure 13(A-H).

20 18. An isolated polypeptide comprising an amino acid sequence encoded by the isolated nucleic acid molecule of Claim 4.

19. An isolated polypeptide comprising an amino acid sequence encoded by the isolated nucleic acid molecule of Claim 5.

25 20. An isolated fusion polypeptide comprising a fusion peptide and an amino acid sequence comprising:

- 30 (a) an amino acid sequence shown in Figures 4(A-AB);
(b) an amino acid sequence shown in Figures 5(A-L);
(c) an amino acid sequence shown in Figures 6(A-K);
(d) an amino acid sequence shown in Figures 7(A-Z);
(e) an amino acid sequence shown in Figures 8(A-S);

- 5
- (f) an amino acid sequence shown in Figures 9(A-X);
 - (g) an amino acid sequence shown in Figures 10(A-V);
 - (h) an amino acid sequence shown in Figures 11(A-I);
 - (i) an amino acid sequence shown in Figures 12(A-G); or
 - (j) the amino acid sequence shown in Figure 13(A-H).

21. An isolated fusion polypeptide comprising a fusion peptide and an amino acid sequence encoded by the isolated nucleic acid molecule of Claim 4.

- 10
22. An isolated fusion polypeptide comprising a fusion peptide and an amino acid sequence encoded by the isolated nucleic acid molecules of Claim 5.

23. An antibody which binds to the isolated polypeptide of Claim 17.

- 15
24. A method for diagnosing a protective sequence-mediated condition, disorder or disease in an individual comprising obtaining a biological sample from said individual; contacting said biological sample with the antibody according to claim 23; wherein if said antibody interacts with said biological sample, but does not interact with a biological sample from a control individual not undergoing a protective sequence-mediated condition, disorder or disease, then a protective sequence-mediated condition, disorder or disease has been diagnosed.
- 20

25. A diagnostic kit for detecting a protective sequence-mediated condition, disorder or disease in an individual comprising a reagent in suitable packaging, wherein said reagent comprises the antibody according to claim 23.

25

26. A method for treating, ameliorating or preventing a protective sequence-mediated condition, disorder or disease in an individual comprising administering to the individual a compound which modulates the function, activity, expression and/or level of a protective sequence in a cell, cells, tissue, organ, organism or individual.

30

27. The method of Claim 26, wherein the compound inhibits the function, activity, expression and/or level of a protective sequence in a cell, cells, tissue, organ, organism or individual.

5 28. The method of Claim 26, wherein the compound enhances or potentiates the function, activity, expression and/or level of a protective sequence in a cell, cells, tissue, organ, organism or individual.

29. The methods of any one of Claims 26-28, wherein the compound is selected
10 from the group consisting of a small organic molecule, an antibody, a ribozyme, an antisense molecule, and combinations thereof.

30. The method of any one of Claims 26-28, wherein the protective sequence-mediated condition, disorder, or disease is a condition, disorder, or disease of the central
15 nervous system.

31. The method of Claim 30, wherein the central nervous system condition is an ischemia-related condition.

20 32. The method of Claim 31, wherein the central nervous system condition is a stroke.

33. The method of Claim 26, wherein the protective sequence encodes a polypeptide comprising:

- 25 (a) an amino acid sequence shown in Figures 4(A-AB);
 (b) an amino acid sequence shown in Figures 5(A-L);
 (c) an amino acid sequence shown in Figures 6(A-K);
 (d) an amino acid sequence shown in Figures 7(A-Z);
 (e) an amino acid sequence shown in Figures 8(A-S);
30 (f) an amino acid sequence shown in Figures 9(A-X);
 (g) an amino acid sequence shown in Figures 10(A-V);

- (h) an amino acid sequence shown in Figures 11(A-D);
- (i) an amino acid sequence shown in Figures 12(A-G); or
- (j) the amino acid sequence shown in Figure 13(A-H).

5 34. The method of Claim 26, wherein the individual is a mammal.

35. The method of Claim 34, wherein the mammal is a human.

10 36. A method for treating, ameliorating, or preventing a protective sequence-mediated condition, disorder or disease in an individual comprising administering to the individual a compound which modulates the expression or activity of a protective sequence product and/or protective sequence regulatory product in the individual.

15 37. The method of Claim 36, wherein the compound inhibits the expression or activity of a protective sequence product and/or protective sequence regulatory product in the individual.

20 38. The method of Claim 36, wherein the compound enhances or potentiates the expression or activity of a protective sequence product and/or protective sequence regulatory product in the individual.

25 39. The method of Claim 36, wherein the compound is selected from the group consisting of a small organic molecule, an antibody, a ribozyme, an antisense molecule, and combinations thereof.

40. The method of Claim 36, wherein the protective sequence-mediated condition, disorder, or disease is a condition, disorder, or disease of the central nervous system.

30 41. The method of Claim 40, wherein the central nervous system condition is an ischemia-related condition.

42. The method of Claim 41, wherein the central nervous system condition is a stroke.

43. The method of Claim 36, wherein the protective sequence product comprises:

- 5 (a) an amino acid sequence shown in Figures 4(A-AB);
- (b) an amino acid sequence shown in Figures 5(A-L);
- (c) an amino acid sequence shown in Figures 6(A-K);
- (d) an amino acid sequence shown in Figures 7(A-Z);
- (e) an amino acid sequence shown in Figures 8(A-S);
- 10 (f) an amino acid sequence shown in Figures 9(A-X);
- (g) an amino acid sequence shown in Figures 10(A-V);
- (h) an amino acid sequence shown in Figures 11(A-I);
- (i) an amino acid sequence shown in Figures 12(A-G); or
- (j) the amino acid sequence shown in Figure 13(A-H).

15 44. The method of Claim 36, wherein the individual is a mammal.

45. The method of Claim 44, wherein the mammal is a human.

20 46. A method for identifying a compound which modulates expression of a protective sequence comprising:

- (a) contacting a test compound to a cell that expresses a protective sequence;
 - (b) measuring a level of protective sequence expression in the cell;
 - (c) comparing the level of protective sequence expression in the cell in the
- 25 presence of the test compound to a level of protective sequence expression in the cell in the absence of the test compound,
- wherein if the level of protective sequence expression in the cell in the presence of the test compound differs from the level of expression of the protective sequence in the cell in the absence of the test compound, a compound that modulates expression of a protective
- 30 sequence is identified.

47. The method of Claim 46, wherein the protective sequence is endogenously expressed within the cell.

48. The method of Claim 46, wherein the protective sequence encodes a polypeptide comprising:

- (a) an amino acid sequence shown in Figures 4(A-AB);
- (b) an amino acid sequence shown in Figures 5(A-L);
- (c) an amino acid sequence shown in Figures 6(A-K);
- (d) an amino acid sequence shown in Figures 7(A-Z);
- 10 (e) an amino acid sequence shown in Figures 8(A-S);
- (f) an amino acid sequence shown in Figures 9(A-X);
- (g) an amino acid sequence shown in Figures 10(A-V);
- (h) an amino acid sequence shown in Figures 11(A-I);
- (i) an amino acid sequence shown in Figures 12(A-G); or
- 15 (j) the amino acid sequence shown in Figure 13(A-H).

49. The method of Claim 46, wherein the protective sequence comprises:

- (a) a nucleic acid sequence shown in Figures 4(A-AB);
- (b) a nucleic acid sequence shown in Figures 5(A-L);
- 20 (c) a nucleic acid sequence shown in Figures 6(A-K);
- (d) a nucleic acid sequence shown in Figures 7(A-Z);
- (e) a nucleic acid sequence shown in Figures 8(A-S);
- (f) a nucleic acid sequence shown in Figures 9(A-X);
- (g) a nucleic acid sequence shown in Figures 10(A-V);
- 25 (h) a nucleic acid sequence shown in Figures 11(A-I);
- (i) a nucleic acid sequence shown in Figures 12(A-G);
- (j) a nucleic acid sequence shown in Figure 13 (A-H); or
- (k) a nucleic acid sequence shown in Figures 1(A-J).

50. A method for identifying a compound which modulates expression, function or activity of a protective sequence product or protective sequence regulatory element comprising:

- 5 (a) contacting a test compound to a cell that expresses a protective sequence product or protective sequence regulatory element;
- (b) measuring a level of protective sequence product or protective sequence regulatory element expression, function or activity in the cell;
- 10 (c) comparing the level of protective sequence product or protective sequence regulatory element expression, function or activity in the cell in the presence of the test compound to a level of protective sequence product or protective sequence regulatory element expression or activity in the cell in the absence of the test compound,
- wherein if the level of protective sequence product or protective sequence regulatory element expression, function or activity in the cell in the presence of the test compound differs from the level of protective sequence product or protective sequence regulatory element
- 15 expression, function or activity in the cell in the absence of the test compound, a compound that modulates expression or activity of a protective sequence product or protective sequence regulatory element is identified.

51. The method of Claim 50, wherein the protective sequence product or

20 protective sequence regulatory element comprises:

- (a) an amino acid sequence shown in Figures 4(A-AB);
- (b) an amino acid sequence shown in Figures 5(A-L);
- (c) an amino acid sequence shown in Figures 6(A-K);
- (d) an amino acid sequence shown in Figures 7(A-Z);
- 25 (e) an amino acid sequence shown in Figures 8(A-S);
- (f) an amino acid sequence shown in Figures 9(A-X);
- (g) an amino acid sequence shown in Figures 10(A-V);
- (h) an amino acid sequence shown in Figures 11(A-I);
- (i) an amino acid sequence shown in Figures 12(A-G); or
- 30 (j) the amino acid sequence shown in Figure 13(A-H).

52. A method for transferring a protective sequence into a cell comprising contacting the cell with a nucleic acid comprising a protective sequence such that the protective sequence is transferred into the cell.

5 53. The method of Claim 52 wherein the protective sequence is expressed in the cell.

54. The method of Claim 52 wherein the protective sequence delays and/or prevents the cell from undergoing cell death.

10

55. A method for modulating the function, activity, expression and/or level of a protective sequence in a cell comprising administering to the cell a compound which modulates the function, activity, expression and/or level of a protective sequence in the cell.

15 56. The method of Claim 55, wherein the compound inhibits the function, activity, expression and/or level of a protective sequence in the cell.

57. The method of Claim 55, wherein the compound enhances or potentiates the function, activity, expression and/or level of a protective sequence in the cell.

20

58. The methods of any one of Claims 55-57, wherein the compound is selected from the group consisting of a small organic molecule, an antibody, a ribozyme, an antisense molecule, and combinations thereof.

25 59. The method of Claim 55, wherein the protective sequence encodes a polypeptide comprising:

- (a) an amino acid sequence shown in Figures 4(A-AB);
- (b) an amino acid sequence shown in Figures 5(A-L);
- (c) an amino acid sequence shown in Figures 6(A-K);
- 30 (d) an amino acid sequence shown in Figures 7(A-Z);
- (e) an amino acid sequence shown in Figures 8(A-S);

- (f) an amino acid sequence shown in Figures 9(A-X);
- (g) an amino acid sequence shown in Figures 10(A-V);
- (h) an amino acid sequence shown in Figures 11(A-I);
- (i) an amino acid sequence shown in Figures 12(A-G); or
- (j) the amino acid sequence shown in Figure 13(A-H).

60. A primer comprising an isolated nucleic acid molecule which hybridizes under highly stringent conditions to:

- (a) a nucleic acid sequence shown in Figures 4(A-AB);
- (b) a nucleic acid sequence shown in Figures 5(A-L);
- (c) a nucleic acid sequence shown in Figures 6(A-K);
- (d) a nucleic acid sequence shown in Figures 7(A-Z);
- (e) a nucleic acid sequence shown in Figures 8(A-S);
- (f) a nucleic acid sequence shown in Figures 9(A-X);
- (g) a nucleic acid sequence shown in Figures 10(A-V);
- (h) a nucleic acid sequence shown in Figures 11(A-I);
- (i) a nucleic acid sequence shown in Figures 12(A-G);
- (j) a nucleic acid sequence shown in Figure 13 (A-H); or
- (k) a nucleic acid sequence shown in Figures 1(A-J).

61. A method for diagnosing a protective sequence-mediated condition, disorder or disease in an individual comprising obtaining a biological sample from said individual; contacting said biological sample with the primer according to claim 60; wherein if said primer interacts with said biological sample, but does not interact with a biological sample from a control individual not undergoing a protective sequence-mediated condition, disorder or disease, then a protective sequence-mediated condition, disorder or disease has been diagnosed.

62. A diagnostic kit for detecting a protective sequence-mediated condition, disorder or disease in an individual comprising a reagent in suitable packaging, wherein said reagent comprises the primer according to claim 60.

tgcacccacg	cgtccgcgga	cgcgtgggta	ggactttgaa	gaatacagtt	tcagtggagt	60
aaactatttt	ttgtgatctg	tttacttata	ttatcctgac	tttaaacatt	ttttagcata	120
agaaaatagt	aaaaaaatat	tttaatgata	taaaatcctt	ggctgctagc	taggagtcgc	180
tctgtgctat	agtagaaaaa	tatggagact	gggagctgtg	tgatctattt	tcaccagtaa	240
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aaagattggt	tttgatgatt	ctcaacatct	ttttctggta	tgtaagactt	tcctcatgaa	360
attcagaaca	ttgccattta	aggaatggca	aagatttttt	ccctaaagtt	aaaagatcaa	420
atatgaaatt	aatataagtt	ataaagtata	tatttcttca	acaataatgt	acagttgaag	480
gtatgtcaaa	aattgacttt	catttataga	aaaaaaagta	aagtaggtaa	ctgtattagt	540
tctctagggg	agctgtaaca	aaataccaaa	aactgggtgg	cttaaacagc	aaaaaaatgt	600
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gctcaagcta	ttctcccacc	tctgcctccc	taagagctgg	gattacaggc	atgagccatc	900
acaccgccc	ctcattttta	tttgattacc	tctgtaaata	cctctgtctc	caaagagat	960
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tatatgcaga	acatcagcct	ttaaagtaat	cttttattag	gaaaatggca	ttcacgattt	1740
gagaagatgg	aagggtgtgg	ggaacagaaa	taaaaaaaaa	aaaaaagggc	ggcc	1794

Figure 1A

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cacatagact	tggcaagagt	aaggagggaa	ctccatagag	acattttacc	tatctcaggg	180
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gacctgaag	aggtcggagc	atcatacaga	ttcctttatt	agcccacatt	ctgatgttcc	720
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ctactgaaca	aaaaaagaaa	aagggcggcc				810

Figure 1B

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Figure 1C

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Figure 1D

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aaaaaaaaaa	aaaaaaaaaa	aaaaagggcg	gcc			1293

Figure 1B

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aaaaaaaaaa	aaaaaaaagg	gcggcc				1466

Figure 1F

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caacgtcatt	gccagtggct	ccgaggactg	cacagtcatt	gtgtgggaga	tcccagatgg	480
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gggcattgtg	gcctggccca	ccacagccca	gaacgtgctg	ctcagtgcag	gttgtgacaa	600
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gcaccagac	acgatctaca	gtgtggactg	gagccgagat	ggaggcctca	tttgtacctc	720
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cctggaggag	ccgctgtccc	tgcaggagct	ggacaccagc	agcgggtgtcc	tgctgccctt	960
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ggaggagaca	gtccaggcca	agtagagccc	cgcagggcct	ccagcagggt	cagccattca	1560
cacccatcca	ctcacctccc	attcccagcc	acatggcaga	gaaaaaaatc	ataataaaat	1620
ggctttat	ttctgtaaaa	aaaaaaaaaa	agggcgcc			1659

Figure 1G

tcgacccacg	cgtccgctct	gccgcagcct	gtgccgccgc	cgcctcctgg	gaagagagga	60
agcgggagag	gagcccacgt	ctcctgtcac	ccaatatctc	cagccgcgca	gtcccgaaga	120
gtgtaagatg	ttcgccctgcg	ccaagctcgc	ctgcaccccc	tctctgatcc	gagctggatc	180
cagagttgca	tacagaccaa	tttctgcac	agtgttatct	cgaccagagg	ctagtaggac	240
tggagagggc	tctacggtat	ttaatggggc	ccagaatggt	gtgtctcagc	taatccaaag	300
ggagtttcag	accagtgcaa	tcagcagaga	cattgatact	gctgccaaat	ttattggtgc	360
aggtgctgca	acagtaggag	tggtggttc	tggtgctggt	attggaacag	tctttggcag	420
ccttatcatt	ggttatgcca	gaaacccttc	gctgaagcag	cagctgttct	catatgctat	480
cctgggattt	gccttgtctg	aagctatggg	tctcttttgt	ttgatggttg	ctttcttgat	540
tttgtttgcc	atgtaacaaa	ttactgcttg	acatgttggc	attcatatta	attacggatg	600
taattctgtg	tatcttactg	tgactccgaa	aactgtagta	ttggtgtcat	gggaatgtac	660
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cc						722

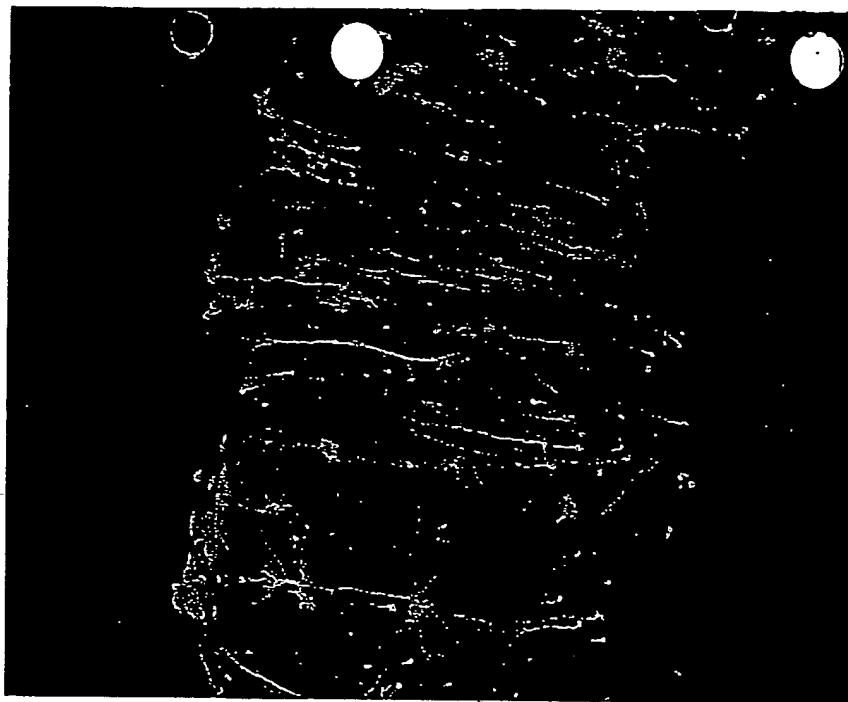
Figure 1H

tcgacccaag	cgtccggatt	tagcaggaag	ctgtgagagc	agtttggttt	ctagcatgaa	60
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ctgggaaagg	gattttcagc	cctcagaatc	gctccacctt	gcagctctcc	ccttctctgt	180
attcctagaa	actgacacat	gctgaacatc	acagcttatt	tcctcatttt	tataatgtcc	240
cttcacaaac	ccagtgtttt	aggagcatga	gtgccgtgtg	tgtgcgtcct	gtcggagccc	300
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ggcc						364

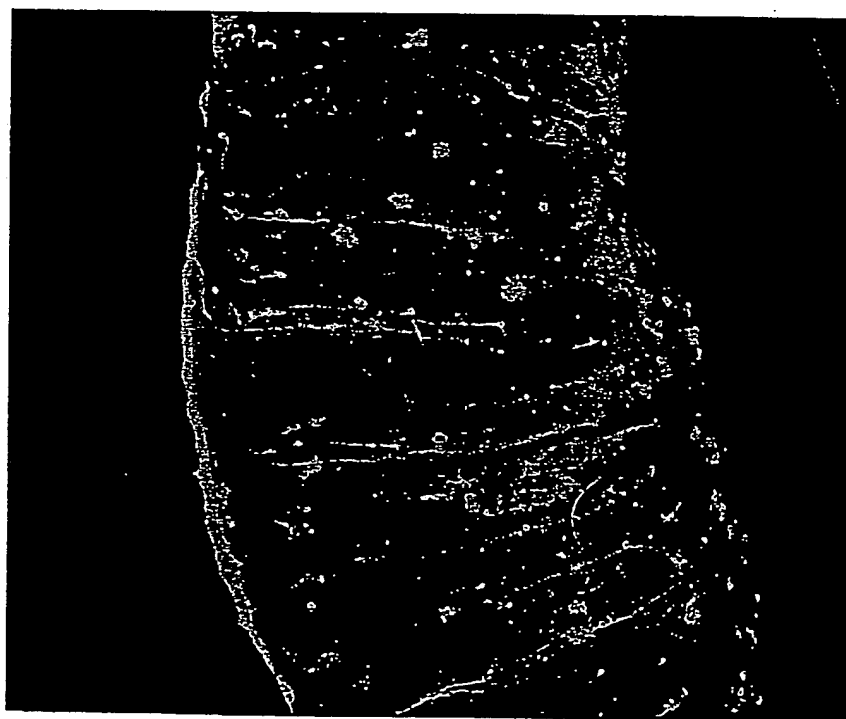
Figure 1I

tccgctctta	gtaagattac	acatgcaagc	atccccgttc	cagtgaagttc	accctctaaa	60
tcaccacgat	caaaagggac	aagcatcaag	cacgcagcaa	tgcagctcaa	aacgcttagc	120
ctagccacac	ccccacggga	aacagcagtg	attaaccttt	agcaataaac	gaaagtttaa	180
ctaagctata	ctaaccacag	ggttggtcaa	tttcgtgcc	gccaccgcgg	tcacacgatt	240
aaccaagtc	aatagaagcc	ggcgtaaaga	gtgttttaga	tcacccctc	ccaataaag	300
ctaaaactca	cctgagttgt	aaaaaactcc	agttgacaca	aaatagacta	cgaaagtggc	360
tttaacatat	ctgaacacac	aatagctaag	acccaaactg	ggattagata	ccccactatg	420
cttagcccta	aacctcaaca	gttaaatcaa	caaaactgct	cgccagaaca	ctacgagcca	480
cagcttaaaa	ctcaaaggac	ctggcggtgc	ttcatacccc	tctagaggag	cctgttctgt	540
aatcgataaa	ccccgatcaa	cctcaccacc	tcttgtcag	cctatatacc	gccatcttca	600
gcaaaccctg	atgaaggcta	caaagtaagc	gcaagtaccc	acgtaaagac	gtaggtcaa	660
ggtgtagccc	atgggggtggc	aagaaatggg	ctacattttc	tacccagaa	aactacgata	720
gcccttatga	aacttaaggg	tcaaggtgg	atttagcagt	aaactgagag	tagagtgctt	780
agttgaacag	ggccctgaag	cgcgtacaca	ccgccgtca	ccctcctcaa	gtatacttca	840
aaggacattt	aactaaaacc	cctacgcatt	tatatagagg	agacaagtcg	taacatggta	900
agtgtactgg	aaagtgcact	tggacgaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	960
aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1020
aaaaaaaaaa	aaaaaaaagg	gcggcc				1046

Figure 1J



Figures 3A and 3B. EGFP positive controls (non-stroked; 1 ug; 1 day post-transfection).



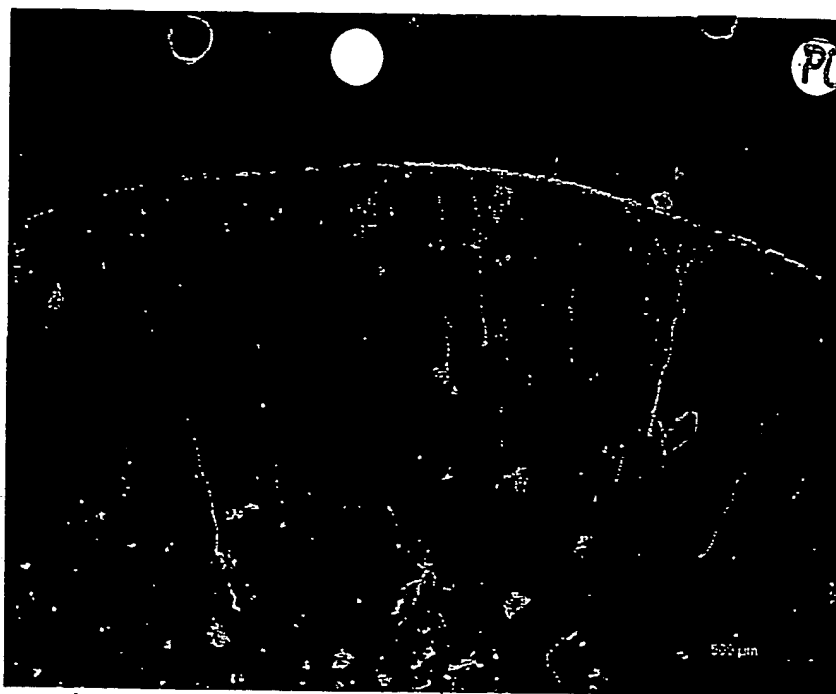
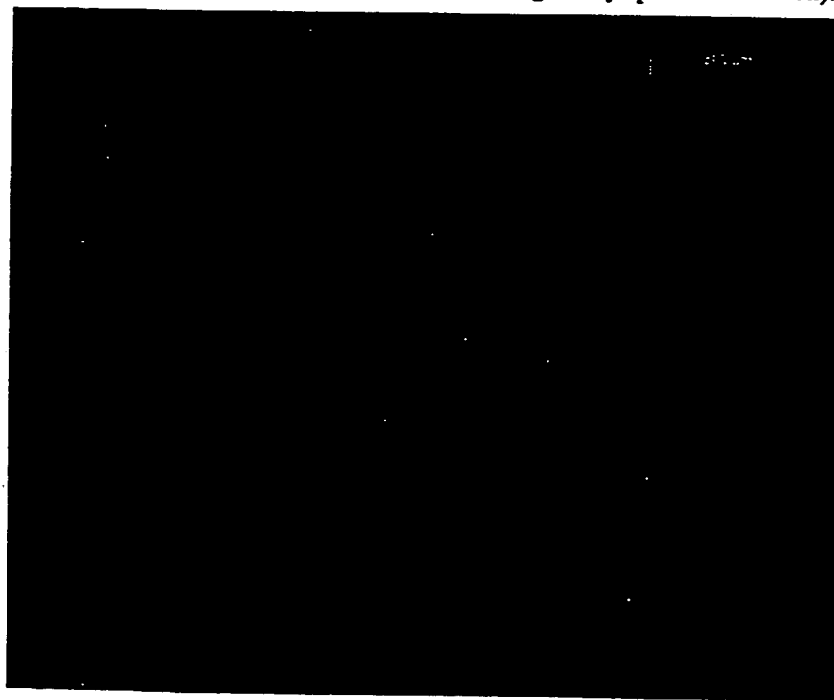


Figure 3C. Bcl-2 positive control (stroked; 1 ug; 3 days post-transfection).

Figure 3D. EGFP-negative control (stroked; 1 ug; 3 days post-transfection).



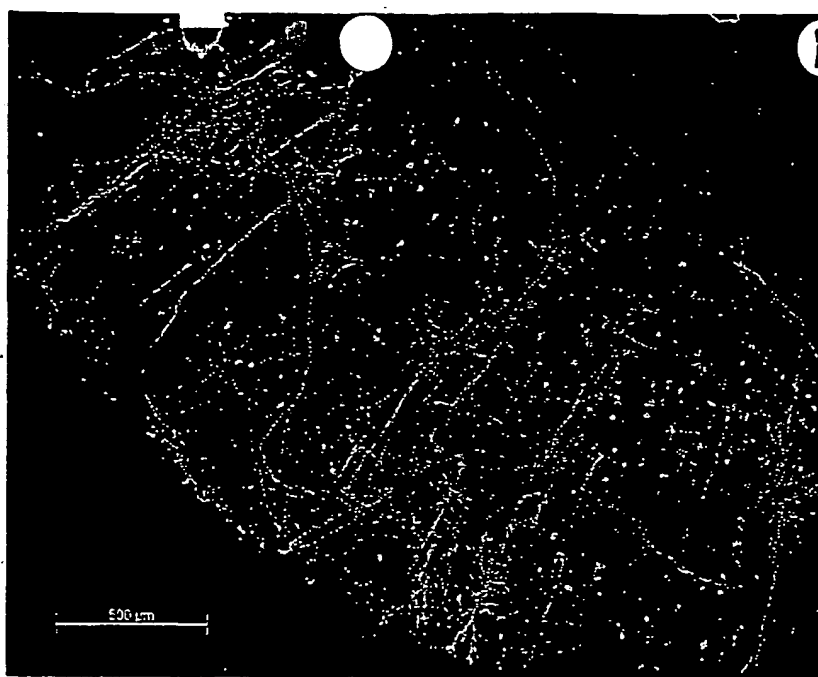


Figure 3E. protective DNA (stroked; 1 ug; 3 days post-transfection).

FIGURE 3F**COMPARISON OF NEURONAL PROTECTION IN STROKED RAT CORTICAL
BRAIN SLICES**

SEQUENCE DESIGNATION	AVERAGE SURVIVING NEURONS PER SLICE (n) @ 3 DAYS POST-STROKE
EGFP Control (negative control)	1.01 (41)
CNI-00718	20.6 (6)
CNI-00722	21 (6)
CNI-00725	14.3 (9)
CNI-00726	19.7 (3)
CNI-00727	17.8 (9)
CNI-00728	10.7 (3)
CNI-00729	13 (3)
CNI-00730	14.7 (3)
CNI-00731	11.7 (3)
CNI-00732	12.7 (3)

FIG
No.

OPEN READING FRAMES FOR CNI-00718

4A	atggagactg ggagctgtgt gatctatttt caccagtaa Met Glu Thr Gly Ser Cys Val Ile Tyr Phe His Gln 1 5 10	39
4B	atgattctca acatcttttt ctggtatgta agactttcct catga Met Ile Leu Asn Ile Phe Phe Trp Tyr Val Arg Leu Ser Ser 1 5 10	45
4C	atgaaattca gaacattgcc atttaaggaa tggcaaagat tttttcccta a Met Lys Phe Arg Thr Leu Pro Phe Lys Glu Trp Gln Arg Phe Phe Pro 1 5 10 15	51
4D	atggcaaaga ttttttcctt aaagttaaaa gatcaaatat ga Met Ala Lys Ile Phe Ser Leu Lys Leu Lys Asp Gln Ile 1 5 10	42
4E	atgaaattaa tataa Met Lys Leu Ile 1	15
4F	atgtacagtt ga Met Tyr Ser 1	12
4G	atgtcaaaaa ttgactttca tttatag Met Ser Lys Ile Asp Phe His Leu 1 5	27

4H	atgtattatc tcacagttct gcagtctaga agtctggaat caaggtgtta g	51
	Met Tyr Tyr Leu Thr Val Leu Gln Ser Arg Ser Leu Glu Ser Arg Cys	
	1 5 10 15	
4I	atgttccagg cctccctcta tggctttag	30
	Met Phe Gln Ala Ser Leu Tyr Gly Leu	
	1 5	
4J	atggcttgta gatggccatc ttcattgtca catggcattc tccctgtagc tctctgtttc	60
	cagaactccc ctttttgtaa ggatatcagt gatattagat tagggtcttc cctaaggacc	120
	catttgacct gcctgggctc aagctattct cccacctctg cctccctaag agctgggatt	180
	acaggcatga gccatcacac ccgcccctca ttttaatttg a	221
	Met Ala Cys Arg Trp Pro Ser Ser Trp Ser His Gly Ile Leu Pro Val	
	1 5 10 15	
	Ala Leu Cys Phe Gln Thr Ser Pro Phe Cys Lys Asp Ile Ser Asp Ile	
	20 25 30	
	Arg Leu Gly Ser Ser Leu Arg Thr Ser Phe Asp Leu Pro Gly Leu Lys	
	35 40 45	
	Leu Phe Ser His Leu Cys Leu Pro Lys Ser Trp Asp Tyr Arg His Glu	
	50 55 60	
	Pro Ser His Pro Pro Leu Ile Leu Ile	
	65 70	
4K	atggccatct tcatgggtcac atggcattct cctgtagct ctctgtttcc agacttcccc	60
	tttttgtaa	69
	Met Ala Ile Phe Met Val Thr Trp His Ser Pro Cys Ser Ser Leu Phe	
	1 5 10 15	
	Pro Asp Phe Pro Phe Leu	
	20	

4L	atggtcacat ggcattctcc ctgtagctct ctgtttccag acttcccctt tttgtaa Met Val Thr Trp His Ser Pro Cys Ser Ser Leu Phe Pro Asp Phe Pro 1 5 10 15 Phe Leu	57
4M	atggcattct ccctgtag Met Ala Phe Ser Leu 1 5	18
4N	atgagccatc acaccgcccc ctcatttttaa Met Ser His His Thr Arg Pro Ser Phe 1 5	30
4O	atgagatttc atcctgagca gctgggggtt aggacttcaa tatatgaatt tgacagggag ggtagaagga gagaacagaa ttcaaccac agcagcaaca atctaatagc ttctgtgag caagcaaaga gaatgttcat tgctagcttc ataggcgcca ttccctattc atacgttact tgtgctctct catattcctt gagtgtttta aattgtaaac attcaagtac aaacaaactt cgcttgatta ccagagataa aaaagaaatg ccttgtaatt tgggtgcatg tgaatgtttt aagtggatac ctgaaaaatt gtacttaaga atggcataa Met Arg Phe His Pro Glu Gln Leu Gly Val Arg Thr Ser Ile Tyr Glu 1 5 10 15 Phe Asp Arg Glu Gly Arg Arg Arg Glu Gln Asn Ser Thr His Ser Ser 20 25 30 Asn Asn Leu Ile Ala Ser Cys Glu Gln Ala Lys Arg Met Phe Ile Val 35 40 45 Ser Leu Ile Gly Ala Ile Pro Tyr Ser Tyr Val Thr Cys Ala Leu Ser 50 55 60 Tyr Ser Leu Ser Val Leu Asn Cys Lys His Ser Ser Thr Asn Lys Leu 65 70 75 80 Arg Leu Ile Thr Arg Asp Lys Lys Glu Met Pro Cys Asn Leu Val Ser 85 90 95 Cys Glu Cys Phe Lys Trp Ile Pro Glu Lys Leu Tyr Leu Arg Met Ala 100 105 110	60 120 180 240 300 339

4P	<p>atgaatttga cagggagggt agaaggagag aacagaattc aaccacagc agcaacaatc 60 taa 63</p> <p>Met Asn Leu Thr Gly Arg Val Glu Gly Glu Asn Arg Ile Gln Pro Thr 1 5 10 15 Ala Ala Thr Ile 20</p>
4Q	<p>atgttcattg tcagtctcat aggcgccatt cctattcat acgttacttg tgctctctca 60 tattccttga gtgtttttaa ttgtaaacad tcaagtacaa acaaacttcg ctgattacc 120 agagataaaa aagaaatgcc ttgtaatttg gtgtcatgtg aatgttttaa gtggatacct 180 gaaaaattgt acttaagaat ggcataa 207</p> <p>Met Phe Ile Val Ser Leu Ile Gly Ala Ile Pro Tyr Ser Tyr Val Thr 1 5 10 15 Cys Ala Leu Ser Tyr Ser Leu Ser Val Leu Asn Cys Lys His Ser Ser 20 25 30 Thr Asn Lys Leu Arg Leu Ile Thr Arg Asp Lys Lys Glu Met Pro Cys 35 40 45 Asn Leu Val Ser Cys Glu Cys Phe Lys Trp Ile Pro Glu Lys Leu Tyr 50 55 60 Leu Arg Met Ala 65</p>
4R	<p>atgccttgta atttgggtgc atgtgaatgt tttaagtgga tacctgaaaa attgtactta 60 agaatggcat aa 72</p> <p>Met Pro Cys Asn Leu Val Ser Cys Glu Cys Phe Lys Trp Ile Pro Glu 1 5 10 15 Lys Leu Tyr Leu Arg Met Ala 20</p>
4S	<p>atgcatagac tgtctatcca ttag 24</p> <p>Met His Arg Leu Ser Ile His 1 5</p>

4T	atgggacctc tcccatctta a	21
	Met Gly Pro Leu Pro Ser	
	1 5	
4U	atgtcctcag gagattgtaa agatgcgttt ccttga	36
	Met Ser Ser Gly Asp Cys Lys Asp Ala Phe Pro	
	1 5 10	
4V	atgcgtttcc ttgattcttt tgctcacact cttccctgtg actatttctt ccttcagggc	60
	tctatttctg ggttgggaga atgctgttcc agcaccaagc agtgtgggta tatatattca	120
	taccaaagag gcaatttgat tgctccttga gttacaaaaa accaaatgtc aatgcctgat	180
	tag	183
	Met Arg Phe Leu Asp Ser Phe Ala His Thr Leu Pro Cys Asp Tyr Phe	
	1 5 10 15	
	Leu Leu Gln Gly Ser Ile Ser Gly Leu Gly Glu Cys Cys Ser Ser Thr	
	20 25 30	
	Lys Gln Cys Gly Tyr Ile Tyr Ser Tyr Gln Arg Gly Asn Leu Ile Val	
	35 40 45	
	Leu Gly Val Thr Lys Asn Gln Met Ser Met Pro Asp	
	50 55 60	
4W	atgctgttcc agcaccaagc agtgtgggta tatatattca taccaaagag gcaatttgat	60
	tgctccttga gttacaaaaa accaaatgtc aatgcctga	99
	Met Leu Phe Gln His Gln Ala Val Trp Val Tyr Ile Phe Ile Pro Lys	
	1 5 10 15	
	Arg Gln Phe Asp Cys Pro Trp Ser Tyr Lys Lys Pro Asn Val Asn Ala	
	20 25 30	
4X	atgtcaatgc ctgattag	18
	Met Ser Met Pro Asp	
	1 5	

4Y	atgcctgatt ag Met Pro Asp 1	12
4Z	atgcagaaca tcagccttta a Met Gln Asn Ile Ser Leu 1 5	21
4AA	atggcattca cgatttga Met Ala Phe Thr Ile 1 5	18
4AB	atggaagggtg gtggggaaca gaaataa Met Glu Gly Gly Gly Glu Gln Lys 1 5	27

FIG
No.

OPEN READING FRAMES FOR CNI-00722

5A	atgagagatc cttaa Met Arg Asp Pro 1	15
5B	atggctcaaa cgctaagag tcagtga Met Ala Gln Thr Leu Met Ser Gln 1 5	27
5C	atgagtcagt ga Met Ser Gln 1	12
5D	atgtgcaggg cactagggaa tacaaggcct tcttcctgg ttgtcttgta a Met Cys Arg Ala Leu Gly Asn Thr Arg Pro Ser Ser Leu Val Val Leu 1 5 10 15	51
5E	atggggttgt ccctccagtc cgagagactg tga Met Gly Leu Ser Leu Gln Ser Glu Arg Leu 1 5 10	33
5F	atgaggccta catag Met Arg Pro Thr 1	15

5G	<p>atgtggtcag gtaaaaatca ggaaccact gaaatcttgg gcaagccacc ctgcctgctt 60 gtgcctcgggt tctctcatat gtcatatata ggaggtgagg actccagctc cacctgcccc 120 aggtgggtgt ggtga 135</p> <p>Met Trp Ser Gly Lys Asn Gln Glu Pro Thr Glu Ile Leu Gly Lys Pro 1 5 10 15 Pro Cys Leu Leu Val Pro Arg Phe Ser His Met Ser Tyr Ile Gly Gly 20 25 30 Glu Asp Ser Ser Ser Thr Cys Pro Arg Trp Val Trp 35 40 36</p>
5H	<p>atgtcatata taggaggtga ggactccagc tccacctgcc ccaggtgggt gtggtga 57</p> <p>Met Ser Tyr Ile Gly Gly Glu Asp Ser Ser Ser Thr Cys Pro Arg Trp 1 5 10 15 Val Trp</p>
5I	<p>atgatgagga aagacaagag gcttgcaagg accctgaaga ggtcggagca tcatacagat 60 tcctttatta gccacattc tgatgttccc tgggtga 96</p> <p>Met Met Arg Lys Asp Lys Arg Leu Ala Arg Thr Leu Lys Arg Ser Glu 1 5 10 15 His His Thr Asp Ser Phe Ile Ser Pro His Ser Asp Val Pro Trp 20 25 30</p>
5J	<p>atgaggaaag acaagaggct tgcaaggacc ctgaagaggt cggagcatca tacagattcc 60 tttattagcc cacattctga tgttccttgg tga 93</p> <p>Met Arg Lys Asp Lys Arg Leu Ala Arg Thr Leu Lys Arg Ser Glu His 1 5 10 15 His Thr Asp Ser Phe Ile Ser Pro His Ser Asp Val Pro Trp 20 25 30</p>

5K	atgttcctcg gtgagacttg cccaagcaa ttgctagtaa atgggggtta a 51
	Met Phe Pro Gly Glu Thr Cys Pro Lys Gln Leu Leu Val Asn Gly Gly
	1 5 10 15
5L	atgggggtta atttcttctc cacctcccta ctgaacaaaa aaagaaaaag ggcggcc 57
	Met Gly Val Asn Phe Phe Ser Thr Ser Leu Leu Asn Lys Lys Arg Lys
	1 5 10 15
	Arg Ala Ala

FIG
No.

OPEN READING FRAMES FOR CNI-00725

6A	atgtcataa ggaaaggta a	21
	Met Leu Ile Arg Lys Gly	
	1 5	
6B	atgtttaacg gccgcggtac cctaaccgtg caaaggtag	39
	Met Phe Asn Gly Arg Gly Thr Leu Thr Val Gln Arg	
	1 5 10	
6C	atgaatggct ccacgagggt tcagctgtct cttactttta accagtga	48
	Met Asn Gly Ser Thr Arg Val Gln Leu Ser Leu Thr Phe Asn Gln	
	1 5 10 15	
6D	atggctccac gagggttcag ctgtctctta cttttaacca gtgaaattga cctgcccgtg	60
	aagaggcggg catga	75
	Met Ala Pro Arg Gly Phe Ser Cys Leu Leu Leu Leu Thr Ser Glu Ile	
	1 5 10 15	
	Asp Leu Pro Val Lys Arg Arg Ala	
	20	
6E	atgacacagc aagacgagaa gaccctatgg agctttaatt tattaatgca aacagtacct	60
	aacaaaccca caggtcctaa actaccaaac ctgcattaa	99
	Met Thr Gln Gln Asp Glu Lys Thr Leu Trp Ser Phe Asn Leu Leu Met	
	1 5 10 15	
	Gln Thr Val Pro Asn Lys Pro Thr Gly Pro Lys Leu Pro Asn Leu His	
	20 25 30	
6F	atggagcttt aa	12
	Met Glu Leu	
	1	

6G	atgcaaacag tacctaacaa acccacaggt cctaaactac caaacctgca ttaa 54
	Met Gln Thr Val Pro Asn Lys Pro Thr Gly Pro Lys Leu Pro Asn Leu
	1 5 10 15
	His
6H	atgctaagac ttcaccagtc aaagcgaact actatactca attga 45
	Met Leu Arg Leu His Gln Ser Lys Arg Thr Thr Ile Leu Asn
	1 5 10
6I	atgttggatc aggacatccc gatggtgcag ccgctattaa aggttcggtt gttcaacgat 60
	taa 63
	Met Leu Asp Gln Asp Ile Pro Met Val Gln Pro Leu Leu Lys Val Arg
	1 5 10 15
	Leu Phe Asn Asp
	20
6J	atgggtgcagc cgctattaaa ggttcggttg ttcaacgatt aa 42
	Met Val Gln Pro Leu Leu Lys Val Arg Leu Phe Asn Asp
	1 5 10
6K	atgatatcat ctcaacttag tattataccc acaccacccc aagaacaggg tttaaaaaaa 60
	aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaagg gcggcc 116
	Met Ile Ser Ser Gln Leu Ser Ile Ile Pro Thr Pro Thr Gln Glu Gln
	1 5 10 15
	Gly Leu Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys
	20 25 30
	Lys Lys Lys Lys Gly Arg
	35

FIG
No.

OPEN READING FRAMES FOR CNI-00726

7A	<p>atggcagcca ccacgggctc gggagtaaaa gtccctcgca atttccgact gttggaagaa 60</p> <p>ctcgaagaag gccagaaagg agtaggagat ggcacagtta gctgggggtct agaagatgac 120</p> <p>gaagacatga cacttacaag atggacaggg atgataattg ggcctccaag aacaatttat 180</p> <p>gaaaaccgaa tatacagcct taaaatagaa tgtggaccta aatacccaga agcaccccc 240</p> <p>tttghtaagat ttgtaacaaa aattaatatg aatggagtaa atagttctaa tggagtgggtg 300</p> <p>gacccaagag ccatatcagt gctagcaaaa tggcagaatt catatagcat caaagttgtc 360</p> <p>ctgcaagagc ttcggcgctc aatgatgtct aaagaaaata tgaaactccc tcagccgccc 420</p> <p>gaaggacagt gttacagcaa ttaa 444</p> <p>Met Ala Ala Thr Thr Gly Ser Gly Val Lys Val Pro Arg Asn Phe Arg</p> <p>1 5 10 - 15</p> <p>Leu Leu Glu Glu Leu Glu Glu Gly Gln Lys Gly Val Gly Asp Gly Thr</p> <p>20 25 30</p> <p>Val Ser Trp Gly Leu Glu Asp Asp Glu Asp Met Thr Leu Thr Arg Trp</p> <p>35 40 45</p> <p>Thr Gly Met Ile Ile Gly Pro Pro Arg Thr Ile Tyr Glu Asn Arg Ile</p> <p>50 55 60</p> <p>Tyr Ser Leu Lys Ile Glu Cys Gly Pro Lys Tyr Pro Glu Ala Pro Pro</p> <p>65 70 75 80</p> <p>Phe Val Arg Phe Val Thr Lys Ile Asn Met Asn Gly Val Asn Ser Ser</p> <p>85 90 95</p> <p>Asn Gly Val Val Asp Pro Arg Ala Ile Ser Val Leu Ala Lys Trp Gln</p> <p>100 105 110</p> <p>Asn Ser Tyr Ser Ile Lys Val Val Leu Gln Glu Leu Arg Arg Leu Met</p> <p>115 120 125</p> <p>Met Ser Lys Glu Asn Met Lys Leu Pro Gln Pro Pro Glu Gly Gln Cys</p> <p>130 135 140</p> <p>Tyr Ser Asn</p> <p>145</p>
7B	<p>atggcacagt tagctggggt ctag 24</p> <p>Met Ala Gln Leu Ala Gly Val</p> <p>1 5</p>

7C	atgacgaaga catga	15
	Met Thr Lys Thr	
	1	
7D	atgacactta caagatggac agggatgata attgggcctc caagaacaat ttatgaaaac	60
	cgaatataca gccttaaaat agaatgtgga cctaaatacc cagaagcacc cccctttgta	120
	agatttgtaa caaaaattaa tatgaatgga gtaaatagtt ctaatggagt ggtggaccca	180
	agagccatat cagtgttagc aaaatggcag aattcatata gcatcaaagt tgcctgcaa	240
	gagcttcggc gcctaatagat gtctaaagaa aatatgaaac tcctcagcc gcccgaggga	300
	cagtgttaca gcaattaa	318
	Met Thr Leu Thr Arg Trp Thr Gly Met Ile Ile Gly Pro Pro Arg Thr	
	1 5 10 15	
	Ile Tyr Glu Asn Arg Ile Tyr Ser Leu Lys Ile Glu Cys Gly Pro Lys	
	20 25 30	
	Tyr Pro Glu Ala Pro Pro Phe Val Arg Phe Val Thr Lys Ile Asn Met	
	35 40 45	
	Asn Gly Val Asn Ser Ser Asn Gly Val Val Asp Pro Arg Ala Ile Ser	
	50 55 60	
	Val Leu Ala Lys Trp Gln Asn Ser Tyr Ser Ile Lys Val Val Leu Gln	
	65 70 75 80	
	Glu Leu Arg Arg Leu Met Met Ser Lys Glu Asn Met Lys Leu Pro Gln	
	85 90 95	
	Pro Pro Glu Gly Gln Cys Tyr Ser Asn	
	100 105	
	101	
7E	atggacaggg atgataattg ggcctccaag aacaatttat ga	42
	Met Asp Arg Asp Asp Asn Trp Ala Ser Lys Asn Asn Leu	
	1 5 10	

7F	<p>atgataattg ggcctccaag aacaatttat gaaaaccgaa tatacagcct taaaatagaa 60</p> <p>tgtggaccta aatacccaga agcaccccc tttgtaagat ttgtaacaaa aattaatatg 120</p> <p>aatggagtaa atagttctaa tggagtggg gacccaagag ccatatcagt gctagcaaaa 180</p> <p>tggcagaatt catatagcat caaagttgtc ctgcaagagc ttcggcgctt aatgatgtct 240</p> <p>aaagaaaata tgaaactccc tcagccgccc gaaggacagt gttacagcaa ttaa 294</p> <p>Met Ile Ile Gly Pro Pro Arg Thr Ile Tyr Glu Asn Arg Ile Tyr Ser</p> <p>1 5 10 15</p> <p>Leu Lys Ile Glu Cys Gly Pro Lys Tyr Pro Glu Ala Pro Pro Phe Val</p> <p>20 25 30</p> <p>Arg Phe Val Thr Lys Ile Asn Met Asn Gly Val Asn Ser Ser Asn Gly</p> <p>35 40 -45</p> <p>Val Val Asp Pro Arg Ala Ile Ser Val Leu Ala Lys Trp Gln Asn Ser</p> <p>50 55 60</p> <p>Tyr Ser Ile Lys Val Val Leu Gln Glu Leu Arg Arg Leu Met Met Ser</p> <p>65 70 75 80</p> <p>Lys Glu Asn Met Lys Leu Pro Gln Pro Pro Glu Gly Gln Cys Tyr Ser</p> <p>85 90 95</p> <p>Asn</p>
7G	<p>atgaaaaccg aatatacagc cttaaaatag 30</p> <p>Met Lys Thr Glu Tyr Thr Ala Leu Lys</p> <p>1 5</p>
7H	<p>atgtggacct aa 12</p> <p>Met Trp Thr</p> <p>1</p>

7I	<p>atgaatggag taaatagttc taatggagtg gtggacccaa gagccatata agtgctagca 60</p> <p>aaatggcaga attcatatag catcaaagtt gtcctgcaag agcttcggcg cctaataatg 120</p> <p>tctaaagaaa atatgaaact ccctcagccg cccgaaggac agtggttacag caattaa 177</p> <p>Met Asn Gly Val Asn Ser Ser Asn Gly Val Val Asp Pro Arg Ala Ile</p> <p>1 5 10 15</p> <p>Ser Val Leu Ala Lys Trp Gln Asn Ser Tyr Ser Ile Lys Val Val Leu</p> <p>20 25 30</p> <p>Gln Glu Leu Arg Arg Leu Met Met Ser Lys Glu Asn Met Lys Leu Pro</p> <p>35 40 45</p> <p>Gln Pro Pro Glu Gly Gln Cys Tyr Ser Asn</p> <p>50 55</p> <p>51</p>
7J	<p>atggagtggt ggaccaaga gccatatcag tgctag 36</p> <p>Met Glu Trp Trp Thr Gln Glu Pro Tyr Gln Cys</p> <p>1 5 10</p>
7K	<p>atggcagaat tcatatag 18</p> <p>Met Ala Glu Phe Ile</p> <p>1 5</p> <p>2</p>
7L	<p>atgatgtcta aagaaaatat gaaactccct cagccgcccg aaggacagtg ttacagcaat 60</p> <p>taa 63</p> <p>Met Met Ser Lys Glu Asn Met Lys Leu Pro Gln Pro Pro Glu Gly Gln</p> <p>1 5 10 15</p> <p>Cys Tyr Ser Asn</p> <p>20</p>
7M	<p>atgtctaaag aaaatatgaa actccctcag ccgcccgaag gacagtgtta cagcaattaa 60</p> <p>Met Ser Lys Glu Asn Met Lys Leu Pro Gln Pro Pro Glu Gly Gln Cys</p> <p>1 5 10 15</p> <p>Tyr Ser Asn</p>

7N	atgaaactcc ctcagccgcc cgaaggacag tgttacagca attaa Met Lys Leu Pro Gln Pro Pro Glu Gly Gln Cys Tyr Ser Asn 1 5 10	45
7O	atgatactaa ttttttcgtc catttga Met Ile Leu Ile Phe Ser Ser Ile 1 5	27
7P	atgccccttc caaacatca tctgtccccc acgtcctccc actcccgcgc ttggccgaag catagattgt aa Met Pro Leu Pro Asn His His Pro Val Pro Thr Leu Leu His Ser Arg 1 5 10 15 Pro Trp Pro Lys His Arg Leu 20	60 72
7Q	atgacacttc cttgctttgg ccagaagcca tcaggtaagg ttggaaagag cctctga Met Thr Leu Pro Cys Phe Gly Gln Lys Pro Ser Gly Lys Val Gly Lys 1 5 10 15 Ser Leu	57
7R	atgaatattg ggtcctcagc cctgccaccc tctgctgtca tcagctga Met Asn Ile Gly Ser Ser Ala Leu Pro Pro Ser Ala Val Ile Ser 1 5 10 15	48
7S	atgcattggt tttag Met His Cys Phe 1	15

7T	<p>atgaagatac ttgtaagcac acatgatccc tctgaattgt tttactttcc tgtaactgct 60 tttgctttta aaaattga 78</p> <p>Met Lys Ile Leu Val Ser Thr His Asp Pro Ser Glu Leu Phe Tyr Phe 1 5 10 15 Pro Val Thr Ala Phe Ala Phe Lys Asn 20 25 21</p>
7U	<p>atgatccctc tgaattgttt tacttttctg taa 33</p> <p>Met Ile Pro Leu Asn Cys Phe Thr Phe Leu 1 5 10</p>
7V	<p>atgccttggg tttgggtgctg ctgctgcttc ccaagatcct cagcagggat taagaaggaa 60 cccgggtgtgc acagcagatc cccgaaattg gtgggcttga cctcctggca aattgctgcg 120 tctttccact tgctgttcag gaccactaaa tgctga 156</p> <p>Met Pro Trp Phe Trp Cys Cys Cys Cys Phe Pro Arg Ser Ser Ala Gly 1 5 10 15 Ile Lys Lys Glu Pro Gly Val His Ser Arg Ser Pro Lys Leu Val Gly 20 25 30 Leu Thr Ser Trp Gln Ile Ala Ala Ser Phe His Leu Leu Phe Arg Thr 35 40 45 Thr Lys Cys 50</p>
7W	<p>atgctgaaat gtggatgcat accgaaataa 30</p> <p>Met Leu Lys Cys Gly Cys Ile Pro Lys 1 5</p>

7X	<p>atgtggatgc ataccgaaat aaaagcaatt cattgtgtac taaaggtttt tttttttttt 60 ttaatttag 69</p> <p>Met Trp Met His Thr Glu Ile Lys Ala Ile His Cys Val Leu Lys Val 1 5 10 15 Phe Phe Phe Phe Leu Ile 20</p>
7Y	<p>atgcataccg aaataaaagc aattcattgt gtactaaagg tttttttttt ttttttaatt 60 tag 63</p> <p>Met His Thr Glu Ile Lys Ala Ile His Cys Val Leu Lys Val Phe Phe 1 5 10 15 Phe Phe Leu Ile 20</p>
7Z	<p>atgtttccat taatcttttt ctgggggggaa aaccttagtt ctaaggattt aacatcctgt 60 aagtga 66</p> <p>Met Phe Pro Leu Ile Phe Phe Trp Gly Glu Asn Leu Ser Ser Lys Asp 1 5 10 15 Leu Thr Ser Cys Lys 20</p>

FIG
No.

OPEN READING FRAMES FOR CNI-00727

8A	atgtgtgtgt gtgtgtgtat gtgtgtgttt ctgagtaagt attga Met Cys Val Cys Val Cys Met Cys Val Phe Leu Ser Lys Tyr 1 5 10	45
8B	atgtgtgtgt ttctgagtaa gtattga Met Cys Val Phe Leu Ser Lys Tyr 1 5	27
8C	atgacgaaat ga Met Thr Lys 1	12
8D	atgagatcaa taggaaatgt gctttttgag gaaattttat tttag Met Arg Ser Ile Gly Asn Val Leu Phe Glu Glu Ile Leu Phe 1 5 10	45
8E	atgtgctttt tgaggaaatt ttatttttagt accaaatggt gccagtga Met Cys Phe Leu Arg Lys Phe Tyr Phe Ser Thr Lys Cys Cys Gln 1 5 10 15	48
8F	atgttgccag tgacaatctt cagttaa Met Leu Pro Val Thr Ile Phe Ser 1 5	27
8G	atgaataagc agcatttttc attgcactta aaaatgtaa Met Asn Lys Gln His Phe Ser Leu His Leu Lys Met 1 5 10	39

8H	atgccactaa tctgtaacat tttaccagtt cagatgcctg taatgtgtga ctttatgtgt	60
	gtctgtgttg ttttgaagag aataaaggaa ataatacttt gcaaactgtt taaacaagtg	120
	tttaaacttc tattggcaac atttattggg ctaagcagtt attga	165
	Met Pro Leu Ile Cys Asn Ile Leu Pro Val Gln Met Pro Val Met Cys 1 5 10 15 Asp Phe Met Cys Val Cys Val Val Leu Lys Arg Ile Lys Glu Ile Ile 20 25 30 Leu Cys Lys Leu Phe Lys Gln Val Phe Lys Leu Leu Leu Ala Thr Phe 35 40 45 Ile Gly Leu Ser Ser Tyr 50	
8I	atgcctgtaa tgtgtgactt tatgtgtgtc tgtgttgttt tgaagagaat aaaggaaata	60
	atactttgca aactgtttaa acaagtgttt aaacttctat tggcaacatt tattgggcta	120
	agcagttatt ga	132
	Met Pro Val Met Cys Asp Phe Met Cys Val Cys Val Val Leu Lys Arg 1 5 10 15 Ile Lys Glu Ile Ile Leu Cys Lys Leu Phe Lys Gln Val Phe Lys Leu 20 25 30 Leu Leu Ala Thr Phe Ile Gly Leu Ser Ser Tyr 35 40	
8J	atgtgtgact ttatgtgtgt ctgtgttgtt ttgaagagaa taaaggaaat aatactttgc	60
	aaactgttta aacaagtgtt taaacttcta ttggcaacat ttattgggct aagcagttat	120
	tga	123
	Met Cys Asp Phe Met Cys Val Cys Val Val Leu Lys Arg Ile Lys Glu 1 5 10 15 Ile Ile Leu Cys Lys Leu Phe Lys Gln Val Phe Lys Leu Leu Leu Ala 20 25 30 Thr Phe Ile Gly Leu Ser Ser Tyr 35 40	

8K	<p>atgtgtgtct gtgttgttt gaagagaata aaggaaataa tactttgcaa actgtttaaa 60</p> <p>caagtgttta aacttctatt ggcaacattt attgggctaa gcagttattg a 111</p> <p>Met Cys Val Cys Val Val Leu Lys Arg Ile Lys Glu Ile Ile Leu Cys</p> <p>1 5 10 15</p> <p>Lys Leu Phe Lys Gln Val Phe Lys Leu Leu Leu Ala Thr Phe Ile Gly</p> <p>20 25 30</p> <p>Leu Ser Ser Tyr</p> <p>35</p>
8L	<p>atgtgtgatg aagcaaaatg tataaagtat gaaatattat acttttacctc tggataa 57</p> <p>Met Cys Asp Glu Ala Lys Cys Ile Lys Tyr Glu Ile Leu Tyr Phe Tyr</p> <p>1 5 10 15</p> <p>Pro Gly</p>
8M	<p>atgaagcaaa atgtataa 18</p> <p>Met Lys Gln Asn Val</p> <p>1 5</p>
8N	<p>atgtataaag tatga 15</p> <p>Met Tyr Lys Val</p> <p>1</p>
8O	<p>atgaaatatt atacttttac cctggataat tattcaggac cccagttggc ccaaataagg 60</p> <p>gcaattttta atcctttgaa attagccagc cagacctaa 99</p> <p>Met Lys Tyr Tyr Thr Phe Thr Leu Asp Asn Tyr Ser Gly Pro Gln Leu</p> <p>1 5 10 15</p> <p>Ala Gln Ile Gly Ala Ile Phe Asn Pro Leu Lys Leu Ala Ser Gln Thr</p> <p>20 25 30</p>

8P	atgctaaggt aa	12
	Met Leu Arg	
	1	
8Q	atgtatctat ttctgtcagg aatgatattt ccaaatgaaa atgtaaagaa cattgggaaa	60
	taa	63
	Met Tyr Leu Phe Leu Ser Gly Met Ile Phe Pro Asn Glu Asn Val Lys	
	1 5 10 15	
	Asn Ile Gly Lys	
	20	
8R	atgatatttc caaatgaaaa tgtaaagaac attgggaaat aa	42
	Met Ile Phe Pro Asn Glu Asn Val Lys Asn Ile Gly Lys	
	1 5 10	
8S	atgaaaatgt aa	12
	Met Lys Met	
	1	

FIG
No.

OPEN READING FRAMES FOR CNI-00728

9A	<p>atgaagagta acagtgtaga ccagactgcc tctctcagat atgtgcctga tttttgtgg 60</p> <p>atacctcccc tgcactggca aaacactatg cttttgggtg ttagactgaa atattttaag 120</p> <p>agtatttaa 129</p> <p>Met Lys Ser Asn Ser Val Asp Gln Thr Ala Ser Leu Arg Tyr Val Pro</p> <p>1 5 10 15</p> <p>Asp Ile Leu Trp Ile Pro Pro Leu His Trp Gln Asn Thr Met Leu Leu</p> <p>20 25 30</p> <p>Gly Val Arg Leu Lys Tyr Phe Lys Ser Ile</p> <p>35 40</p>
9B	<p>atgtgcctga tttttgtgg atacctcccc tgcactggca aaacactatg cttttgggtg 60</p> <p>ttagactga 69</p> <p>Met Cys Leu Ile Phe Cys Gly Tyr Leu Pro Cys Thr Gly Lys Thr Leu</p> <p>1 5 10 15</p> <p>Cys Phe Trp Val Leu Asp</p> <p>20</p>
9C	<p>atgcttttgg gtgtagact gaaatatttt aagagtattt aa 42</p> <p>Met Leu Leu Gly Val Arg Leu Lys Tyr Phe Lys Ser Ile</p> <p>1 5 10</p>
9D	<p>atggaaatgt atcttatgaa tagagacata ttaaaataa 39</p> <p>Met Glu Met Tyr Leu Met Asn Arg Asp Ile Leu Lys</p> <p>1 5 10</p>
9E	<p>atgtatctta tgaatagaga catattaaaa taa 33</p> <p>Met Tyr Leu Met Asn Arg Asp Ile Leu Lys</p> <p>1 5 10</p>

9F	atgaatagag acatattaaa ataa Met Asn Arg Asp Ile Leu Lys 1 5	24
9G	atgtttacat cttag Met Phe Thr Ser 1	15
9H	atggtttctg gagacaaata a Met Val Ser Gly Asp Lys 1 5	21
9I	atgatttatt ttttgactaa atgtgcaatt tcttatcact ag Met Ile Tyr Phe Leu Thr Lys Cys Ala Ile Ser Tyr His 1 5 10	42
9J	atgtgcaatt tcttatcact agataacttt cagtatcagt ggtggttact tattacttaa Met Cys Asn Phe Leu Ser Leu Asp Asn Phe Gln Tyr Gln Trp Trp Leu 1 5 10 15 Leu Ile Thr	60
9K	atgtcgactt gctaa Met Ser Thr Cys 1	15
9L	atgtcttttt ttttagtgc ccaaagatat cttagataa Met Ser Phe Phe Leu Val Ser Gln Arg Tyr Leu Arg 1 5 10	39

9M	<p>atgaggcaac attttcttga gataattacc caagtttcat ccatgttgaa tggtaaaaa 60 tatttctgtg aaactaacag gaagatattt tcagataact ag 102</p> <p>Met Arg Gln His Phe Leu Glu Ile Ile Thr Gln Val Ser Ser Met Leu 1 5 10 15 Asn Gly Thr Lys Tyr Phe Cys Glu Thr Asn Arg Lys Ile Phe Ser Asp 20 25 30 Asn</p>
9N	<p>atgttgaatg gtacaaaata tttctgtgaa actaacagga agatattttc agataactag 60</p> <p>Met Leu Asn Gly Thr Lys Tyr Phe Cys Glu Thr Asn Arg Lys Ile Phe 1 5 10 15 Ser Asp Asn</p>
9O	<p>atggtacaaa atatttctgt gaaactaaca ggaagatatt ttcagataac taggataact 60 tgttgctttg ttaccagcc taattga 87</p> <p>Met Val Gln Asn Ile Ser Val Lys Leu Thr Gly Arg Tyr Phe Gln Ile 1 5 10 15 Thr Arg Ile Thr Cys Cys Phe Val Thr Gln Pro Asn 20 25</p>
9P	<p>atgcttgttt caaagaacca acagaaaaaa aagctaagaa aactgagaac taacattaaa 60 aaaattaaat ttagaataag aatgatttct ttaattgtgc ctttttttct ttggtctaaa 120 acattattaa atttttgtaa atattttgat ttaatgtgc ttagatcctc attattttaa 180</p> <p>Met Leu Val Ser Lys Asn Gln Gln Lys Lys Lys Leu Arg Lys Leu Arg 1 5 10 15 Thr Asn Ile Lys Lys Ile Lys Phe Arg Ile Arg Met Ile Ser Leu Ile 20 25 30 Cys Pro Phe Phe Leu Trp Ser Lys Thr Leu Leu Asn Phe Cys Lys Tyr 35 40 45 Phe Asp Leu Met Cys Leu Arg Ser Ser Leu Phe 50 55</p>

9Q	<p>atgatttctt taatttgtcc ttttttctt tggcttaaaa cattattaaa tttttgtaaa 60</p> <p>tattttgatt taatgtgtct tagatcctca ttattttaa 99</p> <p>Met Ile Ser Leu Ile Cys Pro Phe Phe Leu Trp Ser Lys Thr Leu Leu</p> <p>1 5 10 15</p> <p>Asn Phe Cys Lys Tyr Phe Asp Leu Met Cys Leu Arg Ser Ser Leu Phe</p> <p>20 25 30</p>
9R	<p>atgtgtctta gatcctcatt attttaa 27</p> <p>Met Cys Leu Arg Ser Ser Leu Phe</p> <p>1 5</p>
9S	<p>atgctaatat gtaaagttca tgccatccag gcatttaaga gcgatcctca tcccttcagc 60</p> <p>aatatgtatt tgagttcaca ctattttctgt tttacagcag ttttgaaaaa cacatactat 120</p> <p>gccaccaatt gtcattatatt ttttagatga 150</p> <p>Met Leu Ile Cys Lys Val His Ala Ile Gln Ala Phe Lys Ser Asp Pro</p> <p>1 5 10 15</p> <p>His Pro Phe Ser Asn Met Tyr Leu Ser Ser His Tyr Phe Cys Phe Thr</p> <p>20 25 30</p> <p>Ala Val Leu Lys Asn Thr Tyr Tyr Ala Thr Asn Cys His Ile Ile Phe</p> <p>35 40 45</p> <p>Arg</p>
9T	<p>atgccatcca ggcatttaag agcgatcctc atcccttcag caatatgtat ttga 54</p> <p>Met Pro Ser Arg His Leu Arg Ala Ile Leu Ile Pro Ser Ala Ile Cys</p> <p>1 5 10 15</p> <p>Ile</p>

9U	<p>atgtatttga gttcacacta tttctgtttt acagcagttt tgaaaaaacac atactatgcc 60</p> <p>accaattgtc atattatttt tagatga 87</p> <p>Met Tyr Leu Ser Ser His Tyr Phe Cys Phe Thr Ala Val Leu Lys Asn</p> <p>1 5 10 15</p> <p>Thr Tyr Tyr Ala Thr Asn Cys His Ile Ile Phe Arg</p> <p>20 25</p>
9V	<p>atgccaccaa ttgtcatatt atttttagat gatgtaacat ag 42</p> <p>Met Pro Pro Ile Val Ile Leu Phe Leu Asp Asp Val Thr</p> <p>1 5 10</p>
9W	<p>atgcctaata cttag 15</p> <p>Met Pro Asn Thr</p> <p>1</p>
9X	<p>atgtcacgag atcattttta cattaaacgt gaaaaaaaaat caaaaaaaaa aaaaaaaaaa 60</p> <p>aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 120</p> <p>aaaaaaaaaa agggcggcc 139</p> <p>Met Ser Arg Asp His Phe Tyr Ile Lys Arg Glu Lys Lys Ser Lys Lys</p> <p>1 5 10 15</p> <p>Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys</p> <p>20 25 30</p> <p>Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Gly Gly</p> <p>35 40 45</p>

FIG
No.

OPEN READING FRAMES FOR CNI-00729

10A	atgagccggc aggtgggtccg ctccagcaag ttccgccacg tgtttggaca gccggccaag	
	60	
	gccgaccagt gctatgaaga tgtgcgcgtc tcacagacca cctgggacag tggettctgt	120
	gctgtcaacc ctaagtttgt ggccctgata tgtgaggcca gcgggggagg ggcccttctg	180
	gtgtgcccc tgggcaagac tggacgtgtg gacaagaatg cgcccacggt ctgtggccac	240
	acagcccctg tgctagacat cgcttggtgc ccgcacaatg acaacgtcat tgccagtggc	300
	ttccaggact gcacagtcag ggtgtgggag atcccagatg ggggcctgat gctgcccctg	360
	cgggagcccc tegtaccct ggagggccac accaagcgtg tgggcattgt ggccctggcac	420
	accacagccc agaacgtgct gctcagtga ggttgtgaca acgtgatcat ggtgtgggac	480
	gtgggcactg gggcgcccat gctgacactg ggcccagagg tgcaccaga cacgatctac	540
	agtgtggact ggagccgaga tggaggcctc atttgtacct cctgccgtga caagcgcgtg	600
	cgcatcatcg agccccgaa aggactgtc gtagctgaga aggaccgtcc ccacgagggg	660
	acccggcccc tgcgtgcagt gtctgtgtcg gaggggaaga tcttgaccac gggcttcagc	720
	cgcatgagtg agcggcaggt ggcgtgtgg gacacaaagc acctggagga gccgctgtcc	780
	ctgcaggagc tggacaccag cagcgggtgc ctgctgcct tctttgacct tgacaccaac	840
	atcgtctacc tctgtggcaa gggtagacgc tcaatccggt actttgagat cacttccgag	900
	gcccccttcc tgcactatct ctccatgttc agttccaagg agtcccagcg gggcatgggc	960
	tacatgcccc aacgtggcct ggagggtgaac aagtgtgaga tgcacaggtt ctacaagctg	1020
	cacgagcgga ggtgtgagcc cattgccatg acagtgcctc gaaagtcgga cctgttccag	1080
	gaggacctgt acccaaccac cgcagggccc gacctgccc tcacggctga ggagtggctg	1140
	gggggtcggg atgctgggcc cctcctcacc tccctcaagg atggctacgt acccccaaag	1200
	agccgggagc tgagggtcaa ccggggcctg gacaccgggc gcaggagggc agcaccagag	1260
	gccagtggca ctcccagctc ggatgcctg tctcggtgagg agggagagat gcggaagctc	1320
	caggccacgg tgcaggagct ccagaagcgc ttggacaggc tggaggagac agtccaggcc	1380
	aagtag	1386
	Met Ser Arg Gln Val Val Arg Ser Ser Lys Phe Arg His Val Phe Gly	
	1 5 10 15	
	Gln Pro Ala Lys Ala Asp Gln Cys Tyr Glu Asp Val Arg Val Ser Gln	
	20 25 30	
	Thr Thr Trp Asp Ser Gly Phe Cys Ala Val Asn Pro Lys Phe Val Ala	
	35 40 45	
	Leu Ile Cys Glu Ala Ser Gly Gly Gly Ala Phe Leu Val Leu Pro Leu	
	50 55 60	
	Gly Lys Thr Gly Arg Val Asp Lys Asn Ala Pro Thr Val Cys Gly His	

65	70	75	80
Thr	Ala	Pro	Val
Leu	Asp	Ile	Ala
Trp	Cys	Pro	His
Asn	Asp	Asn	Val
85	90	95	
Ile	Ala	Ser	Gly
Ser	Glu	Asp	Cys
Thr	Val	Met	Val
Trp	Glu	Ile	Pro
100	105	110	
Asp	Gly	Gly	Leu
Met	Leu	Pro	Leu
Arg	Glu	Pro	Val
Val	Thr	Leu	Glu
115	120	125	
Gly	His	Thr	Lys
Arg	Val	Gly	Ile
Val	Ala	Trp	His
Thr	Thr	Ala	Gln
130	135	140	
Asn	Val	Leu	Leu
Ser	Ala	Gly	Cys
Asp	Asn	Val	Ile
Met	Val	Trp	Asp
145	150	155	160
Val	Gly	Thr	Gly
Ala	Ala	Met	Leu
Thr	Leu	Gly	Pro
Glu	Val	His	Pro
165	170	175	
Asp	Thr	Ile	Tyr
Ser	Val	Asp	Trp
Ser	Arg	Asp	Gly
Gly	Gly	Leu	Ile
Cys			
180	185	190	
Thr	Ser	Cys	Arg
Asp	Lys	Arg	Val
Arg	Ile	Ile	Glu
Pro	Arg	Lys	Gly
195	200	205	
Thr	Val	Val	Ala
Glu	Lys	Asp	Arg
Pro	His	Glu	Gly
Thr	Arg	Pro	Val
210	215	220	
Arg	Ala	Val	Phe
Val	Ser	Glu	Gly
Lys	Ile	Leu	Thr
Thr	Gly	Phe	Ser
225	230	235	240
Arg	Met	Ser	Glu
Arg	Gln	Val	Ala
Leu	Trp	Asp	Thr
Lys	His	Leu	Glu
245	250	255	
Glu	Pro	Leu	Ser
Leu	Gln	Glu	Leu
Asp	Thr	Ser	Ser
Gly	Val	Leu	Leu
260	265	270	
Pro	Phe	Phe	Asp
Pro	Asp	Thr	Asn
Ile	Val	Tyr	Leu
Cys	Gly	Lys	Gly
275	280	285	
Asp	Ser	Ser	Ile
Arg	Tyr	Phe	Glu
Ile	Thr	Ser	Glu
Ala	Pro	Phe	Leu
290	295	300	
His	Tyr	Leu	Ser
Met	Phe	Ser	Ser
Lys	Glu	Ser	Gln
Arg	Gly	Met	Gly
305	310	315	320
Tyr	Met	Pro	Lys
Arg	Gly	Leu	Glu
Val	Asn	Lys	Cys
Glu	Ile	Ala	Arg
325	330	335	
Phe	Tyr	Lys	Leu
His	Glu	Arg	Arg
Cys	Glu	Pro	Ile
Ala	Met	Thr	Val
340	345	350	
Pro	Arg	Lys	Ser
Asp	Leu	Phe	Gln
Glu	Asp	Leu	Tyr
Pro	Pro	Thr	Ala
355	360	365	

	<p>Gly Pro Asp Pro Ala Leu Thr Ala Glu Glu Trp Leu Gly Gly Arg Asp 370 375 380</p> <p>Ala Gly Pro Leu Leu Ile Ser Leu Lys Asp Gly Tyr Val Pro Pro Lys 385 390 395 400</p> <p>Ser Arg Glu Leu Arg Val Asn Arg Gly Leu Asp Thr Gly Arg Arg Arg 405 410 415</p> <p>Ala Ala Pro Glu Ala Ser Gly Thr Pro Ser Ser Asp Ala Val Ser Arg 420 425 430</p> <p>Leu Glu Glu Glu Met Arg Lys Leu Gln Ala Thr Val Gln Glu Leu Gln 435 440 445</p> <p>Lys Arg Leu Asp Arg Leu Glu Glu Thr Val Gln Ala Lys 450 455 460</p>	
10B	<p>atgaagatgt ggcgctctca cagaccacct gggacagtgg cttctgtgct gtcaacccta 60 agtttgtggc cctga 75</p> <p>Met Lys Met Cys Ala Ser His Arg Pro Pro Gly Thr Val Ala Ser Val 1 5 10 15</p> <p>Leu Ser Thr Leu Ser Leu Trp Pro 20</p>	
10C	<p>atgtgcgcgt ctcacagacc acctgggaca gtggcttctg tgctgtcaac cctaagtttg 60 tggccctga 69</p> <p>Met Cys Ala Ser His Arg Pro Pro Gly Thr Val Ala Ser Val Leu Ser 1 5 10 15</p> <p>Thr Leu Ser Leu Trp Pro 20</p>	
10D	<p>atgcgcccac ggtctgtggc cacacagccc ctgtgctag 39</p> <p>Met Arg Pro Arg Ser Val Ala Thr Gln Pro Leu Cys 1 5 10</p>	

10E	atgacaacgt cattgccagt ggctccgagg actgcacagt catggtgtgg gagatcccag	60
	atgggggcct ga	72
	Met Thr Thr Ser Leu Pro Val Ala Pro Arg Thr Ala Gln Ser Trp Cys	
	1 5 10 15	
	Gly Arg Ser Gln Met Gly Ala	
	20	
10F	atggtgtggg agatcccaga tgggggcctg atgctgcccc tgcgggagcc cgtcgtcacc	60
	ctggagggcc acaccaagcg tgtgggcatt gtggcctggc acaccacagc ccagaacgtg	120
	ctgctcagtg caggttgtga caacgtgatc atggtgtggg acgtgggcac tggggcgggc	180
	atgctgacac tggggccaga ggtgcaccca gacacgatct acagtgtgga ctggagccga	240
	gatggaggcc tcatttgtac ctctgccgt gacaagcgcg tgcgcatcat cgagccccgc	300
	aaaggcactg tcgtagctga gaaggaccgt cccacgagg ggaccggcc cgtgcgtgca	360
	gtgttcgtgt cggaggggaa gatcctgacc acgggcttca gccgcatgag tgagcggcag	420
	gtggcgctgt gggacacaaa gcacctggag gagccgctgt cctgcagga gctggacacc	480
	agcagcggtg tcctgctgcc cttctttgac cctgacacca acatcgtcta cctctgtggc	540
	aagggtgaca gctcaatccg gtactttgag atcacttccg agggcccttt cctgcactat	600
	ctctccatgt tcagttccaa ggagtcccag cggggcatgg gctacatgcc caaacgtggc	660
	ctggaggtga acaagtgtga gatcgccagg ttctacaagc tgcacgagcg gaggtgtgag	720
	cccattgcca tgacagtgcc tcgaaagtcg gacctgttcc aggaggacct gtaccacccc	780
	accgcagggc ccgaccctgc cctcacggct gaggagtggc tggggggtcg ggatgctggg	840
	cccctctca tctccetcaa ggatggctac gtaccccaa agagccggga gctgagggtc	900
	aaccggggcc tggacaccgg gcgcaggagg gcagcaccag aggccagtgg cactcccagc	960
	tcggatgccg tgtctcggct ggaggaggag atcggaagc tccaggccac ggtgcaggag	1020
	ctccagaagc gcttgacag gctggaggag acagtccagg ccaagtag	1068
	Met Val Trp Glu Ile Pro Asp Gly Gly Leu Met Leu Pro Leu Arg Glu	
	1 5 10 15	
	Pro Val Val Thr Leu Glu Gly His Thr Lys Arg Val Gly Ile Val Ala	
	20 25 30	
	Trp His Thr Thr Ala Gln Asn Val Leu Leu Ser Ala Gly Cys Asp Asn	
	35 40 45	
	Val Ile Met Val Trp Asp Val Gly Thr Gly Ala Ala Met Leu Thr Leu	
	50 55 60	
	Gly Pro Glu Val His Pro Asp Thr Ile Tyr Ser Val Asp Trp Ser Arg	
	65 70 75 80	

Asp	Gly	Gly	Leu	Ile	Cys	Thr	Ser	Cys	Arg	Asp	Lys	Arg	Val	Arg	Ile
				85					90					95	
Ile	Glu	Pro	Arg	Lys	Gly	Thr	Val	Val	Ala	Glu	Lys	Asp	Arg	Pro	His
				100					105					110	
Glu	Gly	Thr	Arg	Pro	Val	Arg	Ala	Val	Phe	Val	Ser	Glu	Gly	Lys	Ile
				115					120					125	
Leu	Thr	Thr	Gly	Phe	Ser	Arg	Met	Ser	Glu	Arg	Gln	Val	Ala	Leu	Trp
				130					135					140	
Asp	Thr	Lys	His	Leu	Glu	Glu	Pro	Leu	Ser	Leu	Gln	Glu	Leu	Asp	Thr
				145					150					155	
Ser	Ser	Gly	Val	Leu	Leu	Pro	Phe	Phe	Asp	Pro	Asp	Thr	Asn	Ile	Val
				165					170					175	
Tyr	Leu	Cys	Gly	Lys	Gly	Asp	Ser	Ser	Ile	Arg	Tyr	Phe	Glu	Ile	Thr
				180					185					190	
Ser	Glu	Ala	Pro	Phe	Leu	His	Tyr	Leu	Ser	Met	Phe	Ser	Ser	Lys	Glu
				195					200					205	
Ser	Gln	Arg	Gly	Met	Gly	Tyr	Met	Pro	Lys	Arg	Gly	Leu	Glu	Val	Asn
				210					215					220	
Lys	Cys	Glu	Ile	Ala	Arg	Phe	Tyr	Lys	Leu	His	Glu	Arg	Arg	Cys	Glu
				225					230					235	
Pro	Ile	Ala	Met	Thr	Val	Pro	Arg	Lys	Ser	Asp	Leu	Phe	Gln	Glu	Asp
				245					250					255	
Leu	Tyr	Pro	Pro	Thr	Ala	Gly	Pro	Asp	Pro	Ala	Leu	Thr	Ala	Glu	Glu
				260					265					270	
Trp	Leu	Gly	Gly	Arg	Asp	Ala	Gly	Pro	Leu	Leu	Ile	Ser	Leu	Lys	Asp
				275					280					285	
Gly	Tyr	Val	Pro	Pro	Lys	Ser	Arg	Glu	Leu	Arg	Val	Asn	Arg	Gly	Leu
				290					295					300	
Asp	Thr	Gly	Arg	Arg	Arg	Ala	Ala	Pro	Glu	Ala	Ser	Gly	Thr	Pro	Ser
				305					310					315	
Ser	Asp	Ala	Val	Ser	Arg	Leu	Glu	Glu	Glu	Met	Arg	Lys	Leu	Gln	Ala
				325					330					335	
Thr	Val	Gln	Glu	Leu	Gln	Lys	Arg	Leu	Asp	Arg	Leu	Glu	Glu	Thr	Val
				340					345					350	
Gln	Ala	Lys													
				355											

10G	atgggggcct ga	12
	Met Gly Ala	
	1	
10H	atgctgcccc tgcgggagcc cgtcgtcacc ctggagggcc acaccaagcg tgtgggcatt	60
	gtggcctggc acaccacagc ccagaacgtg ctgctcagtg caggttgtga caacgtgate	120
	atggtgtggg acgtgggcac tggggcggcc atgctgacac tgggcccaga ggtgcaccca	180
	gacacgatct acagtgtgga ctggagccga gatggaggcc tcatttgtac ctcctgccgt	240
	gacaagcgcg tgcgcatcat cgagccccgc aaaggcactg tcgtagctga gaaggaccgt	300
	ccccacgagg ggacccgcc cgtgcgtgca gtgttcgtgt cggaggggaa gatcctgacc	360
	acgggcttca gcgcgatgag tgagcggcag gtggcgctgt gggacacaaa gcacctggag	420
	gagccgctgt cctgcagga gctggacacc agcagcggtg tcctgctgcc cttctttgac	480
	cctgacacca acatcgtcta cctctgtggc aagggtgaca gctcaatccg gtactttgag	540
	atcacttccg agggcccttt cctgcactat ctctccatgt tcagttccaa ggagtccag	600
	cggggcatgg gctacatgcc caaacgtggc ctggagggtga acaagtgtga gatcgccagg	660
	ttctacaagc tgcacgagcg gaggtgtgag ccatttgcca tgacagtgcc tcgaaagtgc	720
	gacctgttcc aggaggacct gtaccacccc accgcagggc ccgaccctgc cctcacggct	780
	gaggagtggc tggggggtcg ggatgctggg cccctcctca tctccctcaa ggatggctac	840
	gtacccccaa agagccggga gctgaggggc aaccggggcc tggacaccgg gcgcaggagg	900
	gcagcaccag agggcagtgg cactcccagc tcggatgccg tgtctcggct ggaggaggag	960
	atgcggaagc tccaggccac ggtgcaggag ctccagaagc gcttgagacag gctggaggag	1020
	acagtccagg ccaagtag	1038
	Met Leu Pro Leu Arg Glu Pro Val Val Thr Leu Glu Gly His Thr Lys	
	1 5 10 15	
	Arg Val Gly Ile Val Ala Trp His Thr Thr Ala Gln Asn Val Leu Leu	
	20 25 30	
	Ser Ala Gly Cys Asp Asn Val Ile Met Val Trp Asp Val Gly Thr Gly	
	35 40 45	
	Ala Ala Met Leu Thr Leu Gly Pro Glu Val His Pro Asp Thr Ile Tyr	
	50 55 60	
	Ser Val Asp Trp Ser Arg Asp Gly Gly Leu Ile Cys Thr Ser Cys Arg	
	65 70 75 80	
	Asp Lys Arg Val Arg Ile Ile Glu Pro Arg Lys Gly Thr Val Val Ala	
	85 90 95	
	Glu Lys Asp Arg Pro His Glu Gly Thr Arg Pro Val Arg Ala Val Phe	

	100	105	110	
	Val Ser Glu Gly Lys Ile Leu Thr Thr Gly Phe Ser Arg Met Ser Glu			
	115	120	125	
	Arg Gln Val Ala Leu Trp Asp Thr Lys His Leu Glu Glu Pro Leu Ser			
	130	135	140	
	Leu Gln Glu Leu Asp Thr Ser Ser Gly Val Leu Leu Pro Phe Phe Asp			
	145	150	155	160
	Pro Asp Thr Asn Ile Val Tyr Leu Cys Gly Lys Gly Asp Ser Ser Ile			
	165	170	175	
	Arg Tyr Phe Glu Ile Thr Ser Glu Ala Pro Phe Leu His Tyr Leu Ser			
	180	185	190	
	Met Phe Ser Ser Lys Glu Ser Gln Arg Gly Met Gly Tyr Met Pro Lys			
	195	200	205	
	Arg Gly Leu Glu Val Asn Lys Cys Glu Ile Ala Arg Phe Tyr Lys Leu			
	210	215	220	
	His Glu Arg Arg Cys Glu Pro Ile Ala Met Thr Val Pro Arg Lys Ser			
	225	230	235	240
	Asp Leu Phe Gln Glu Asp Leu Tyr Pro Pro Thr Ala Gly Pro Asp Pro			
	245	250	255	
	Ala Leu Thr Ala Glu Glu Trp Leu Gly Gly Arg Asp Ala Gly Pro Leu			
	260	265	270	
	Leu Ile Ser Leu Lys Asp Gly Tyr Val Pro Pro Lys Ser Arg Glu Leu			
	275	280	285	
	Arg Val Asn Arg Gly Leu Asp Thr Gly Arg Arg Arg Ala Ala Pro Glu			
	290	295	300	
	Ala Ser Gly Thr Pro Ser Ser Asp Ala Val Ser Arg Leu Glu Glu Glu			
	305	310	315	320
	Met Arg Lys Leu Gln Ala Thr Val Gln Glu Leu Gln Lys Arg Leu Asp			
	325	330	335	
	Arg Leu Glu Glu Thr Val Gln Ala Lys			
	340	345		
	341			
10I	atggtgtggg acgtgggcac tggggcggcc atgctgacac tgggccccaga ggtgcaccca	60		
	gacacgatct acagtgtgga ctggagccga gatggaggcc tcatttgtac ctctgccgt	120		
	gacaagcgcg tgcgcatcat cgagccccgc aaaggcactg tcgtagctga gaaggaccgt	180		
	ccccacgagg ggaccgggcc cgtgcgtgca gtgttcgtgt cggaggggaa gatcctgacc	240		
	acgggcttca gccgcatgag tgagcggcag gtggcgctgt gggacacaaa gcacctggag	300		
	gagccgctgt ccctgcagga gctggacacc agcagcggtg tcctgctgcc cttctttgac	360		

cctgacacca acatcgtcta cctctgtggc aaggggtgaca gctcaatccg gtactttgag	420
atcacttccg aggccctttt cctgcactat ctctccatgt tcagttccaa ggagtcccag	480
cggggcatgg gctacatgcc caaacgtggc ctggaggtga acaagtgtga gatcgccagg	540
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gacctgttcc aggaggacct gtaccacccc accgcagggc ccgaccctgc cctcacggct	660
gaggagtggc tggggggtcg ggatgctggg cccctcctca tctccctcaa ggatggctac	720
gtacccccaa agagccggga gctgagggtc aaccggggcc tggacaccgg gcgcaggagg	780
gcagcaccag aggccagtgg cactcccagc tcggatgccg tgtctcggct ggaggaggag	840
atgcggaagc tccaggccac ggtgcaggag ctccagaagc gcttggacag gctggaggag	900
acagtccagg ccaagtag	918
Met Val Trp Asp Val Gly Thr Gly Ala Ala Met Leu Thr Leu Gly Pro	
1 5 10 15	
Glu Val His Pro Asp Thr Ile Tyr Ser Val Asp Trp Ser Arg Asp Gly	
20 25 30	
Gly Leu Ile Cys Thr Ser Cys Arg Asp Lys Arg Val Arg Ile Ile Glu	
35 40 45	
Pro Arg Lys Gly Thr Val Val Ala Glu Lys Asp Arg Pro His Glu Gly	
50 55 60	
Thr Arg Pro Val Arg Ala Val Phe Val Ser Glu Gly Lys Ile Leu Thr	
65 70 75 80	
Thr Gly Phe Ser Arg Met Ser Glu Arg Gln Val Ala Leu Trp Asp Thr	
85 90 95	
Lys His Leu Glu Glu Pro Leu Ser Leu Gln Glu Leu Asp Thr Ser Ser	
100 105 110	
Gly Val Leu Leu Pro Phe Phe Asp Pro Asp Thr Asn Ile Val Tyr Leu	
115 120 125	
Cys Gly Lys Gly Asp Ser Ser Ile Arg Tyr Phe Glu Ile Thr Ser Glu	
130 135 140	
Ala Pro Phe Leu His Tyr Leu Ser Met Phe Ser Ser Lys Glu Ser Gln	
145 150 155 160	
Arg Gly Met Gly Tyr Met Pro Lys Arg Gly Leu Glu Val Asn Lys Cys	
165 170 175	
Glu Ile Ala Arg Phe Tyr Lys Leu His Glu Arg Arg Cys Glu Pro Ile	
180 185 190	
Ala Met Thr Val Pro Arg Lys Ser Asp Leu Phe Gln Glu Asp Leu Tyr	
195 200 205	

	Pro Pro Thr Ala Gly Pro Asp Pro Ala Leu Thr Ala Glu Glu Trp Leu 210 215 220 Gly Gly Arg Asp Ala Gly Pro Leu Leu Ile Ser Leu Lys Asp Gly Tyr 225 230 235 240 Val Pro Pro Lys Ser Arg Glu Leu Arg Val Asn Arg Gly Leu Asp Thr 245 250 255 Gly Arg Arg Arg Ala Ala Pro Glu Ala Ser Gly Thr Pro Ser Ser Asp 260 265 270 Ala Val Ser Arg Leu Glu Glu Glu Met Arg Lys Leu Gln Ala Thr Val 275 280 285 Gln Glu Leu Gln Lys Arg Leu Asp Arg Leu Glu Glu Thr Val Gln Ala 290 295 300 Lys 305	
10J	atgctgacac tgggcccaga ggtgcaccca gacacgatct acagtgtgga ctggagccga gatggaggcc tcatttgtac ctctgccgt gacaagcgcg tgcgcatcat cgagccccgc aaaggcactg tcgtagctga gaaggaccgt cccacagagg ggacccggcc cgtgcgtgca gtgttcgtgt cggaggggaa gatcctgacc acgggcttca gccgcatgag tgagcggcag gtggcgctgt gggacacaaa gcacctggag gagccgctgt ccctgcagga gctggacacc agcagcggtg tcctgctgcc ctctcttgac cctgacacca acatcgtcta cctctgtggc aagggtgaca gctcaatccg gtactttgag atcacttccg aggcccttt cctgcactat ctctccatgt tcagttccaa ggagtcccag cggggcatgg gctacatgcc caaacgtggc ctggaggtga acaagtgtga gatcgccagg ttctacaagc tgcacgagcg gaggtgtgag cccattgcca tgacagtgcc tcgaaagtgc gacctgttcc aggaggacct gtaccacccc accgcagggc ccgacctgc cctcacggct gaggagtggc tggggggtcg ggatgctggg cccctcctca tctccctcaa ggatggctac gtacccccaa agagccggga gctgagggtc aaccggggcc tggacaccgg gcgcaggagg gcagcaccag aggccagtgg cactcccagc tcggatgccg tgtctcggct ggaggaggag atgcggaagc tccaggccac ggtgcaggag ctccagaagc gcttggacag gctggaggag acagtccagg ccaagtag Met Leu Thr Leu Gly Pro Glu Val His Pro Asp Thr Ile Tyr Ser Val 1 5 10 15 Asp Trp Ser Arg Asp Gly Gly Leu Ile Cys Thr Ser Cys Arg Asp Lys 20 25 30 Arg Val Arg Ile Ile Glu Pro Arg Lys Gly Thr Val Val Ala Glu Lys 35 40 45	60 120 180 240 300 360 420 480 540 600 660 720 780 840 888

	Asp Arg Pro His Glu Gly Thr Arg Pro Val Arg Ala Val Phe Val Ser	
	50 55 60	
	Glu Gly Lys Ile Leu Thr Thr Gly Phe Ser Arg Met Ser Glu Arg Gln	
	65 70 75 80	
	Val Ala Leu Trp Asp Thr Lys His Leu Glu Glu Pro Leu Ser Leu Gln	
	85 90 95	
	Glu Leu Asp Thr Ser Ser Gly Val Leu Leu Pro Phe Phe Asp Pro Asp	
	100 105 110	
	Thr Asn Ile Val Tyr Leu Cys Gly Lys Gly Asp Ser Ser Ile Arg Tyr	
	115 120 125	
	Phe Glu Ile Thr Ser Glu Ala Pro Phe Leu His Tyr Leu Ser Met Phe	
	130 135 140	
	Ser Ser Lys Glu Ser Gln Arg Gly Met Gly Tyr Met Pro Lys Arg Gly	
	145 150 155 160	
	Leu Glu Val Asn Lys Cys Glu Ile Ala Arg Phe Tyr Lys Leu His Glu	
	165 170 175	
	Arg Arg Cys Glu Pro Ile Ala Met Thr Val Pro Arg Lys Ser Asp Leu	
	180 185 190	
	Phe Gln Glu Asp Leu Tyr Pro Pro Thr Ala Gly Pro Asp Pro Ala Leu	
	195 200 205	
	Thr Ala Glu Glu Trp Leu Gly Gly Arg Asp Ala Gly Pro Leu Leu Ile	
	210 215 220	
	Ser Leu Lys Asp Gly Tyr Val Pro Pro Lys Ser Arg Glu Leu Arg Val	
	225 230 235 240	
	Asn Arg Gly Leu Asp Thr Gly Arg Arg Arg Ala Ala Pro Glu Ala Ser	
	245 250 255	
	Gly Thr Pro Ser Ser Asp Ala Val Ser Arg Leu Glu Glu Glu Met Arg	
	260 265 270	
	Lys Leu Gln Ala Thr Val Gln Glu Leu Gln Lys Arg Leu Asp Arg Leu	
	275 280 285	
	Glu Glu Thr Val Gln Ala Lys	
	290 295	
10K	atggaggcct catttgtagc tcctgccgtg acaagcgcgt gcgcacatc gagccccgca	60
	aaggcactgt cgtag	75
	Met Glu Ala Ser Phe Val Pro Pro Ala Val Thr Ser Ala Cys Ala Ser	
	1 5 10 15	

	Ser Ser Pro Ala Lys Ala Leu Ser	
	20	
10L	atgagtgagc ggcaggtggc gctgtgggac acaaagcacc tggaggagcc gctgtccctg	60
	caggagctgg acaccagcag cgggtgcctg ctgcccttct ttgacctga caccaacatc	120
	gtctacctct gtggcaaggg tgacagctca atccggtact ttgagatcac ttccgaggcc	180
	cctttcctgc actatctctc catgttcagt tccaaggagt cccagcgggg catgggctac	240
	atgccccaaac gtggcctgga ggtgaacaag tgtgagatcg ccaggttcta caagctgcac	300
	gagcggaggt gtgagcccat tgccatgaca gtgcctcgaa agtcggacct gttccaggag	360
	gacctgtacc caccaccgc agggcccgac cctgccctca cggctgagga gtggctgggg	420
	ggtcgggatg ctggggccct cctcatctcc ctcaaggatg gctacgtacc cccaaagagc	480
	cgggagctga gggtaaccg gggcctggac accgggcgca ggagggcagc accagaggcc	540
	agtggcactc ccagctcgga tgccgtgtct cggctggagg aggagatgcy gaagctccag	600
	gccacggtgc aggagctcca gaagcgcttg gacaggctgg aggagacagt ccaggccaag	660
	tag	663
	Met Ser Glu Arg Gln Val Ala Leu Trp Asp Thr Lys His Leu Glu Glu	
	1 5 10 15	
	Pro Leu Ser Leu Gln Glu Leu Asp Thr Ser Ser Gly Val Leu Leu Pro	
	20 25 30	
	Phe Phe Asp Pro Asp Thr Asn Ile Val Tyr Leu Cys Gly Lys Gly Asp	
	35 40 45	
	Ser Ser Ile Arg Tyr Phe Glu Ile Thr Ser Glu Ala Pro Phe Leu His	
	50 55 60	
	Tyr Leu Ser Met Phe Ser Ser Lys Glu Ser Gln Arg Gly Met Gly Tyr	
	65 70 75 80	
	Met Pro Lys Arg Gly Leu Glu Val Asn Lys Cys Glu Ile Ala Arg Phe	
	85 90 95	
	Tyr Lys Leu His Glu Arg Arg Cys Glu Pro Ile Ala Met Thr Val Pro	
	100 105 110	
	Arg Lys Ser Asp Leu Phe Gln Glu Asp Leu Tyr Pro Pro Thr Ala Gly	
	115 120 125	
	Pro Asp Pro Ala Leu Thr Ala Glu Glu Trp Leu Gly Gly Arg Asp Ala	
	130 135 140	
	Gly Pro Leu Leu Ile Ser Leu Lys Asp Gly Tyr Val Pro Pro Lys Ser	
	145 150 155 160	
	Arg Glu Leu Arg Val Asn Arg Gly Leu Asp Thr Gly Arg Arg Arg Ala	
	165 170 175	

	Ala Pro Glu Ala Ser Gly Thr Pro Ser Ser Asp Ala Val Ser Arg Leu	
	180 185 190	
	Glu Glu Glu Met Arg Lys Leu Gln Ala Thr Val Gln Glu Leu Gln Lys	195
	200 205	
	Arg Leu Asp Arg Leu Glu Glu Thr Val Gln Ala Lys	
	210 215 220	
10M	atgttcagtt ccaaggagtc ccagcggggc atgggctaca tgcccaaacg tggcctggag	60
	gtgaacaagt gtgagatcgc caggttctac aagctgcacg agcggagggtg tgagcccatt	120
	gccatgacag tgcttcgaaa gtccggacctg ttccaggagg acctgtaccc acccaccgca	180
	gggcccagacc ctgccctcac ggctgaggag tggctggggg gtcgggatgc tgggcccctc	240
	ctcatctccc tcaaggatgg ctacgtaccc ccaaagagcc gggagctgag ggtcaaccgg	300
	ggcctggaca ccgggcgcag gagggcagca ccagaggcca gtggcactcc cagctcggat	360
	gccgtgtctc ggctggagga ggagatgcgg aagctccagg ccacggtgca ggagctccag	420
	aagcgcttgg acaggctgga ggagacagtc caggccaagt ag	462
	Met Phe Ser Ser Lys Glu Ser Gln Arg Gly Met Gly Tyr Met Pro Lys	
	1 5 10 15	
	Arg Gly Leu Glu Val Asn Lys Cys Glu Ile Ala Arg Phe Tyr Lys Leu	
	20 25 30	
	His Glu Arg Arg Cys Glu Pro Ile Ala Met Thr Val Pro Arg Lys Ser	
	35 40 45	
	Asp Leu Phe Gln Glu Asp Leu Tyr Pro Pro Thr Ala Gly Pro Asp Pro	
	50 55 60	
	Ala Leu Thr Ala Glu Glu Trp Leu Gly Gly Arg Asp Ala Gly Pro Leu	
	65 70 75 80	
	Leu Ile Ser Leu Lys Asp Gly Tyr Val Pro Pro Lys Ser Arg Glu Leu	
	85 90 95	
	Arg Val Asn Arg Gly Leu Asp Thr Gly Arg Arg Arg Ala Ala Pro Glu	
	100 105 110	
	Ala Ser Gly Thr Pro Ser Ser Asp Ala Val Ser Arg Leu Glu Glu Glu	
	115 120 125	
	Met Arg Lys Leu Gln Ala Thr Val Gln Glu Leu Gln Lys Arg Leu Asp	
	130 135 140	
	Arg Leu Glu Glu Thr Val Gln Ala Lys	
	145 150	

10N	atgggctaca tgcccaaacy tggcctggag gtgaacaagt gtgagatcgc caggttctac 60
	aagctgcacg agcggaggtg tgagcccat gccatgacag tgcctcgaaa gtcggacctg 120
	ttccaggagg acctgtaccc acccaccgca gggcccgacc ctgccctcac ggctgaggag 180
	tggctggggg gtcgggatgc tgggcccctc ctcattctcc tcaaggatgg ctacgtaccc 240
	ccaaagagcc gggagctgag ggtcaaccgg ggcctggaca ccgggcgcag gagggcagca 300
	ccagaggcca gtggcactcc cagctcggat gccgtgtctc ggctggagga ggagatgcgg 360
	aagctccagg ccacggtgca ggagctccag aagcgcttgg acaggctgga ggagacagtc 420
	caggccaagt ag 432
	Met Gly Tyr Met Pro Lys Arg Gly Leu Glu Val Asn Lys Cys Glu Ile
	1 5 10 15
	Ala Arg Phe Tyr Lys Leu His Glu Arg Arg Cys Glu Pro Ile Ala Met
	20 25 30
	Thr Val Pro Arg Lys Ser Asp Leu Phe Gln Glu Asp Leu Tyr Pro Pro
	35 40 45
	Thr Ala Gly Pro Asp Pro Ala Leu Thr Ala Glu Glu Trp Leu Gly Gly
	50 55 60
	Arg Asp Ala Gly Pro Leu Leu Ile Ser Leu Lys Asp Gly Tyr Val Pro
	65 70 75 80
	Pro Lys Ser Arg Glu Leu Arg Val Asn Arg Gly Leu Asp Thr Gly Arg
	85 90 95
	Arg Arg Ala Ala Pro Glu Ala Ser Gly Thr Pro Ser Ser Asp Ala Val
	100 105 110
	Ser Arg Leu Glu Glu Glu Met Arg Lys Leu Gln Ala Thr Val Gln Glu
	115 120 125
	Leu Gln Lys Arg Leu Asp Arg Leu Glu Glu Thr Val Gln Ala Lys
	130 135 140
100	atgcccaaac gtggcctgga ggtgaacaag tgtgagatcg ccaggttcta caagctgcac 60
	gagcggaggt gtgagcccat tgccatgaca gtgcctcgaa agtcggacct gttccaggag 120
	gacctgtacc caccaccgc agggcccgac cctgccctca cggtgagga gtggctgggg 180
	ggtcgggatg ctggggccct cctcatctcc ctcaaggatg gctacgtacc cccaaagagc 240
	cgggagctga ggtcaaccg gggcctggac accgggcgca ggagggcagc accagaggcc 300
	agtggcactc ccagctcgga tgccgtgtct cggctggagg aggagatgcg gaagctccag 360
	gccacggtgc aggagctcca gaagcgcttg gacaggtgg aggagacagt ccaggccaag 420
	tag 423

	Met Pro Lys Arg Gly Leu Glu Val Asn Lys Cys Glu Ile Ala Arg Phe 1 5 10 15 Tyr Lys Leu His Glu Arg Arg Cys Glu Pro Ile Ala Met Thr Val Pro 20 25 30 Arg Lys Ser Asp Leu Phe Gln Glu Asp Leu Tyr Pro Pro Thr Ala Gly 35 40 45 Pro Asp Pro Ala Leu Thr Ala Glu Glu Trp Leu Gly Gly Arg Asp Ala 50 55 60 Gly Pro Leu Leu Ile Ser Leu Lys Asp Gly Tyr Val Pro Pro Lys Ser 65 70 75 80 Arg Glu Leu Arg Val Asn Arg Gly Leu Asp Thr Gly Arg Arg Arg Ala 85 90 95 Ala Pro Glu Ala Ser Gly Thr Pro Ser Ser Asp Ala Val Ser Arg Leu 100 105 110 Glu Glu Glu Met Arg Lys Leu Gln Ala Thr Val Gln Glu Leu Gln Lys 115 120 125 Arg Leu Asp Arg Leu Glu Glu Thr Val Gln Ala Lys 130 135 140
10P	atgacagtgc ctcgaaagtc ggacctgttc caggaggacc tgtaccacc caccgcaggg 60 cccgaccctg ccctcacggc tgaggagtgg ctgggggggc gggatgctgg gccctcctc 120 atctccctca aggatggcta cgtaccccca aagagccggg agctgagggt caaccggggc 180 ctggacaccg ggcgcaggag ggcagcacca gaggccagtg gcactcccag ctcggtatgcc 240 gtgtctcggc tggaggagga gatgcggaag ctccaggcca cgggtgcagga gctccagaag 300 cgcttggaaca ggctggagga gacagtccag gccaaagtag 339 Met Thr Val Pro Arg Lys Ser Asp Leu Phe Gln Glu Asp Leu Tyr Pro 1 5 10 15 Pro Thr Ala Gly Pro Asp Pro Ala Leu Thr Ala Glu Glu Trp Leu Gly 20 25 30 Gly Arg Asp Ala Gly Pro Leu Leu Ile Ser Leu Lys Asp Gly Tyr Val 35 40 45 Pro Pro Lys Ser Arg Glu Leu Arg Val Asn Arg Gly Leu Asp Thr Gly 50 55 60 Arg Arg Arg Ala Ala Pro Glu Ala Ser Gly Thr Pro Ser Ser Asp Ala 65 70 75 80 Val Ser Arg Leu Glu Glu Glu Met Arg Lys Leu Gln Ala Thr Val Gln

	<p>85 90 95</p> <p>Glu Leu Gln Lys Arg Leu Asp Arg Leu Glu Glu Thr Val Gln Ala Lys</p> <p>100 105 110</p>
10Q	<p>atgctggggc cctcctcatc tccctcaagg atggctacgt acccccaaag agccgggagc 60</p> <p>tga 63</p> <p>Met Leu Gly Pro Ser Ser Ser Pro Ser Arg Met Ala Thr Tyr Pro Gln</p> <p>1 5 10 15</p> <p>Arg Ala Gly Ser</p> <p>20</p>
10R	<p>atggctacgt acccccaaag agccgggagc tga 33</p> <p>Met Ala Thr Tyr Pro Gln Arg Ala Gly Ser</p> <p>1 5 10</p>
10S	<p>atgccgtgtc tcggctggag gaggagatgc ggaagctcca ggccacggtg caggagctcc 60</p> <p>agaagcgctt ggacaggctg gaggagacag tccaggccaa gtagagcccc gcagggcctc 120</p> <p>cagcagggtc agccattcac acccatccac tcacctcca ttcccagcca catggcagag 180</p> <p>aaaaaaatca taataaaatg gctttatttt ctggtaaaaa aaaaaaaaaa gggcggcc 238</p> <p>Met Pro Cys Leu Gly Trp Arg Arg Arg Cys Gly Ser Ser Arg Pro Arg</p> <p>1 5 10 15</p> <p>Cys Arg Ser Ser Arg Ser Ala Trp Thr Gly Trp Arg Arg Gln Ser Arg</p> <p>20 25 30</p> <p>Pro Ser Arg Ala Pro Gln Gly Leu Gln Gln Gly Gln Pro Phe Thr Pro</p> <p>35 40 45</p> <p>Ile His Ser Pro Pro Ile Pro Ser His Met Ala Glu Lys Lys Ile Ile</p> <p>50 55 60</p> <p>Ile Lys Trp Leu Tyr Phe Leu Val Lys Lys Lys Lys Lys Gly Gly</p> <p>65 70 75</p>

10T	atgcggaagc tccaggccac ggtgcaggag ctccagaagc gcttggacag gctggaggag acagtccagg ccaagtag	60 78
	Met Arg Lys Leu Gln Ala Thr Val Gln Glu Leu Gln Lys Arg Leu Asp 1 5 10 15 Arg Leu Glu Glu Thr Val Gln Ala Lys 20 25	
10U	atggcagaga aaaaaatcat aataaaatgg ctttatatttc tggtaaaaaa aaaaaaaaag ggcggcc	60
	Met Ala Glu Lys Lys Ile Ile Ile Lys Trp Leu Tyr Phe Leu Val Lys 1 5 10 15 Lys Lys Lys Lys Gly Gly 20	
10V	atggcctttat tttctggtaa aaaaaaaaaa aaagggcggc c	41
	Met Ala Leu Phe Ser Gly Lys Lys Lys Lys Lys Gly Arg 1 5 10	

FIG
No.

OPEN READING FRAMES FOR CNI-00730

11A	atgttcgcct ggcceaagct cgctgcacc cctctctga tccgagctgg atccagagtt 60
	gcatacagac caatttctgc atcagtgtta tctcgaccag aggctagtag gactggagag 120
	ggctctacgg tatttaatgg ggcccagaat ggtgtgtctc agctaatacca aaggagagttt 180
	cagaccagtg caatcagcag agacattgat actgctgcca aatttattgg tgcaggtgct 240
	gcaacagtag gagtggctgg ttctgggtgct ggtattggaa cagtctttgg cagccttatac 300
	attgggttatg ccagaaaccc ttcgctgaag cagcagctgt tctcatatgc tctcctggga 360
	tttgcttgt ctgaagctat gggctctctt tgtttgatgg ttgctttctt gattttgttt 420
	gccatgtaa 429
	Met Phe Ala Cys Ala Lys Leu Ala Cys Thr Pro Ser Leu Ile Arg Ala
	1 5 10 15
	Gly Ser Arg Val Ala Tyr Arg Pro Ile Ser Ala Ser Val Leu Ser Arg
	20 25 30
	Pro Glu Ala Ser Arg Thr Gly Glu Gly Ser Thr Val Phe Asn Gly Ala
	35 40 45
	Gln Asn Gly Val Ser Gln Leu Ile Gln Arg Glu Phe Gln Thr Ser Ala
	50 55 60
	Ile Ser Arg Asp Ile Asp Thr Ala Ala Lys Phe Ile Gly Ala Gly Ala
	65 70 75 80
	Ala Thr Val Gly Val Ala Gly Ser Gly Ala Gly Ile Gly Thr Val Phe
	85 90 95
	Gly Ser Leu Ile Ile Gly Tyr Ala Arg Asn Pro Ser Leu Lys Gln Gln
	100 105 110
	Leu Phe Ser Tyr Ala Ile Leu Gly Phe Ala Leu Ser Glu Ala Met Gly
	115 120 125
	Leu Phe Cys Leu Met Val Ala Phe Leu Ile Leu Phe Ala Met
	130 135 140
11B	atggggccca gaatggtgtg tctcagctaa 30
	Met Gly Pro Arg Met Val Cys Leu Ser
	1 5

11C	atggtgtgtc tcagctaa	18
	Met Val Cys Leu Ser	
	1 5	
11D	atgccagaaa cccttcgtg a	21
	Met Pro Glu Thr Leu Arg	
	1 5	
11E	atgctatcct gggatttgcc ttgtctgaag ctatgggtct cttttgtttg a	51
	Met Leu Ser Trp Asp Leu Pro Cys Leu Lys Leu Trp Val Ser Phe Val	
	1 5 10 15	
11F	atgggtctct tttgtttgat ggttgctttc ttgattttgt ttgcatgta a	51
	Met Gly Leu Phe Cys Leu Met Val Ala Phe Leu Ile Leu Phe Ala Met	
	1 5 10 15	
11G	atggttgctt tcttgatttt gtttgccatg taa	33
	Met Val Ala Phe Leu Ile Leu Phe Ala Met	
	1 5 10	
11..	atgttggcat tcatattaat tacggatgta attctgtgta tcttactgtg a	51
	Met Leu Ala Phe Ile Leu Ile Thr Asp Val Ile Leu Cys Ile Leu Leu	
	1 5 10 15	

111	atgggaatgt acgttatctc caaagtcatt tcattaaaga tgaaaacttt aaaaaaaaaa	60
	aaaaaagggc ggcc	74
	Met Gly Met Tyr Val Ile Ser Lys Val Ile Ser Leu Lys Met Lys Thr	
	1 5 10 15	
	Leu Lys Lys Lys Lys Lys Gly Arg	
	20	

FIG
No.

OPEN READING FRAMES FOR CNI-00731

12A	atgaagacag agccccaccc tcagatgcac atgagctggc gggattga	48
	Met Lys Thr Glu Pro His Pro Gln Met His Met Ser Trp Arg Asp	
	1 5 10 15	
12B	atgcacatga gctggcggga ttga	24
	Met His Met Ser Trp Arg Asp	
	1 5	
12C	atgagctggc gggattga	18
	Met Ser Trp Arg Asp	
	1 5	
	2	
12D	atgctgtctt cgtactggga aagggatttt cagccctcag aatcgctcca ccttcagct	60
	ctccccttct ctgtattcct agaaactgac acatgctga	99
	Met Leu Ser Ser Tyr Trp Glu Arg Asp Phe Gln Pro Ser Glu Ser Leu	
	1 5 10 15	
	His Leu Ala Ala Leu Pro Phe Ser Val Phe Leu Glu Thr Asp Thr Cys	
	20 25 30	
12E	atgctgaaca tcacagctta tttcctcatt tttataatgt cccttcacaa acccagtgtt	60
	ttaggagcat ga	72
	Met Leu Asn Ile Thr Ala Tyr Phe Leu Ile Phe Ile Met Ser Leu His	
	1 5 10 15	
	Lys Pro Ser Val Leu Gly Ala	
	20	
12F	atgtcccttc acaaaccag tggttttagga gcatga	36
	Met Ser Leu His Lys Pro Ser Val Leu Gly Ala	
	1 5 10	

12G	atgagtgccg tgtgtgtgcg tcctgtcgga gccctgtctc ctctctctgt aataaactca	60
	tttctagcag aaaaaaaaaa aaaaaaaaaa gggcggcc	98
	Met Ser Ala Val Cys Val Arg Pro Val Gly Ala Leu Ser Pro Leu Ser	
	1 5 10 15	
	Val Ile Asn Ser Phe Leu Ala Glu Lys Lys Lys Lys Lys Lys Gly Arg	
	20 25 30	

FIG
No.

OPEN READING FRAMES FOR CNI-00732

13A	atgcaagcat ccccggtcca gtga	24
	Met Gln Ala Ser Pro Phe Gln	
	1 5	
13B	atgcagctca aaacgcttag cctagccaca cccccacggg aaacagcagt gattaacctt	60
	tag	63
	Met Gln Leu Lys Thr Leu Ser Leu Ala Thr Pro Pro Arg Glu Thr Ala	
	1 5 10 15	
	Val Ile Asn Leu	
	20	
13C	atgcttagcc ctaaactca acagttaa at caacaaaact gctcgccaga acactacgag	60
	ccacagctta aaactcaaag gacctggcgg tgcttcatac ccctctag	108
	Met Leu Ser Pro Lys Pro Gln Gln Leu Asn Gln Gln Asn Cys Ser Pro	
	1 5 10 15	
	Glu His Tyr Glu Pro Gln Leu Lys Thr Gln Arg Thr Trp Arg Cys Phe	
	20 25 30	
	Ile Pro Leu	
	35	
13D	atgaaggcta caaagtaa	18
	Met Lys Ala Thr Lys	
	1 5	
13E	atgggggtggc aagaaatggg ctacattttc tacccagaa aactacgata g	51
	Met Gly Trp Gln Glu Met Gly Tyr Ile Phe Tyr Pro Arg Lys Leu Arg	
	1 5 10 15	

SEQUENCE LISTING

<110> Shawn Barney
Mary Beth Thomas
Stuart D. Portbury
Kasturi Puranam
Lawrence C. Katz
Donald C. Lo

<120> COMPOSITIONS AND METHODS FOR DIAGNOSING
AND TREATING CONDITIONS, DISORDERS, OR DISEASES INVOLVING
CELL DEATH

<130> 10001-0006-999

<160> 342

<170> FastSEQ for Windows Version 4.0

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<211> 1794

<212> DNA

<213> Homo Sapiens

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agaaaatagt	aaaaaaatat	tttaatgata	taaaatcctt	ggctgctagc	taggagtcgc	180
tctgtgctat	agtagaaaaa	tatggagact	gggagctgtg	tgatctat	tcaccagtaa	240
ctgggtgact	ttaaaaggcc	tgtaacttgt	acttgtctac	ttttatccag	ttctacactg	300
aaagattgtt	tttgatgatt	ctcaacatct	ttttctggta	tgtaagactt	tcctcatgaa	360
attcagaaca	ttgccattta	aggaatggca	aagatttttt	ccctaaagtt	aaaagatcaa	420
atatgaaatt	aatataagtt	ataaagtata	tatttcttca	acaataatgt	acagttgaag	480
gtatgtcaaa	aattgacttt	catttataga	aaaaaaagta	aagtaggtaa	ctgtattagt	540
tctctagggg	agctgtaaca	aaataccaaa	aactgggtgg	cttaaacagc	aaaaaaatgt	600
attatctcac	agttctgcag	tctagaagtc	tggaatcaag	gtgttagtag	ggctggttct	660
ttctgagggc	tggaaggca	ggatatgttc	caggcctccc	tctatggctt	gtagatggcc	720
atcttcatgg	tcacatggca	ttctccctgt	agctctctgt	ttccagactt	cccctttttg	780
taaggatata	agtgatatta	gattagggtc	ttccctaagg	acctcatttg	acctgcctgg	840
gctcaagcta	ttctcccacc	tctgcctccc	taagagctgg	gattacaggc	atgagccatc	900
acaccgccc	ctcattttta	tttgattacc	tctgtaaata	cctctgtctc	caaatgagat	960
ttcatcctga	gcagctgggg	gttaggactt	caatatatga	atttgacagg	gagggtagaa	1020
ggagagaaca	gaattcaacc	cacagcagca	acaatcta	agcttcctgt	gagcaagcaa	1080
agagaatgtt	cattgtcagt	ctcataggcg	ccattcccta	ttcatacgtt	acttgtgtct	1140
tctcatattc	cttgagtgtt	ttaaattgta	aacattcaag	tacaaacaaa	cttcgcttga	1200
ttaccagaga	taaaaaagaa	atgccttgta	atttggtgtc	atgtgaatgt	tttaagtggg	1260
tacctgaaaa	attgtactta	agaatggcat	aagagctttc	tgattttcat	tttacttcca	1320
ttaaagggga	aaatatgcat	agactgtcta	tccattagcc	agaacaatgg	gacctctccc	1380
atcttaaaat	aaaagccaaa	ataatctggc	caccaggaag	aaagggtaga	gcttgggaat	1440
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actatttcct	ccttcagggc	tctatttctg	ggttgggaga	atgctgttcc	agcaccaagc	1560
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accaaattgtc	aatgcctgat	tagggaatac	aacaataaaa	gtaaaaataa	tttaggagta	1680
tatatgcaga	acatcagcct	ttaaagta	cttttattag	gaaaatggca	ttcacgattt	1740
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1 5 10

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<212> DNA
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<210> 5
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1 5 10

<210> 6
<211> 51
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<213> Homo Sapiens

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<210> 7
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<212> PRT
<213> Homo Sapiens

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1 5 10 15

<210> 8
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<210> 9
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<212> PRT
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1 5 10

<210> 10
<211> 15
<212> DNA
<213> Homo Sapiens

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<212> PRT
<213> Homo Sapiens

<400> 11
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<210> 12
<211> 12
<212> DNA
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<400> 12
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12

<210> 13
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<212> PRT
<213> Homo Sapiens

<400> 13
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1

<210> 14
<211> 27
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<400> 14
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<210> 15
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<212> PRT
<213> Homo Sapiens

<400> 15
Met Ser Lys Ile Asp Phe His Leu
1 5

<210> 16
<211> 51
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51

<210> 17
<211> 16
<212> PRT
<213> Homo Sapiens

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Met Tyr Tyr Leu Thr Val Leu Gln Ser Arg Ser Leu Glu Ser Arg Cys
1 5 10 15

<210> 18
<211> 30

<212> DNA

<213> Homo Sapiens

<400> 18

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30

<210> 19

<211> 9

<212> PRT

<213> Homo Sapiens

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Met Phe Gln Ala Ser Leu Tyr Gly Leu

1

5

<210> 20

<211> 221

<212> DNA

<213> Homo Sapiens

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catttgacct	gcctgggctc	aagctattct	cccacctctg	cctccctaag	agctgggatt	180
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<211> 73

<212> PRT

<213> Homo Sapiens

<400> 21

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1				5					10					15	
Ala	Leu	Cys	Phe	Gln	Thr	Ser	Pro	Phe	Cys	Lys	Asp	Ile	Ser	Asp	Ile
		20					25					30			
Arg	Leu	Gly	Ser	Ser	Leu	Arg	Thr	Ser	Phe	Asp	Leu	Pro	Gly	Leu	Lys
		35				40						45			
Leu	Phe	Ser	His	Leu	Cys	Leu	Pro	Lys	Ser	Trp	Asp	Tyr	Arg	His	Glu
	50				55						60				
Pro	Ser	His	Pro	Pro	Leu	Ile	Leu	Ile							
65					70										

<210> 22

<211> 69

<212> DNA

<213> Homo Sapiens

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tttttgtaa						69

<210> 23

<211> 22

<212> PRT

<213> Homo Sapiens

<400> 23

Met	Ala	Ile	Phe	Met	Val	Thr	Trp	His	Ser	Pro	Cys	Ser	Ser	Leu	Phe
1				5					10					15	
Pro	Asp	Phe	Pro	Phe	Leu										
			20												

<210> 24

<211> 57

<212> DNA

<213> Homo Sapiens

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<210> 25

<211> 18

<212> PRT

<213> Homo Sapiens

<400> 25

Met Val Thr Trp His Ser Pro Cys Ser Ser Leu Phe Pro Asp Phe Pro

1

5

10

15

Phe Leu

<210> 26

<211> 18

<212> DNA

<213> Homo Sapiens

<400> 26

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<210> 27

<211> 5

<212> PRT

<213> Homo Sapiens

<400> 27

Met Ala Phe Ser Leu

1

5

<210> 28

<211> 30

<212> DNA

<213> Homo Sapiens

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atgagccatc acacccgccc ctcattttaa 30

<210> 29

<211> 9

<212> PRT

<213> Homo Sapiens

<400> 29

Met Ser His His Thr Arg Pro Ser Phe

1

5

<210> 30

<211> 339

<212> DNA

<213> Homo Sapiens

<400> 30

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ggtagaagga	gagaacagaa	ttcaaccac	agcagcaaca	atctaatagc	ttcctgtgag	120
caagcaaaga	gaatgttcat	tgtcagtctc	ataggcgcca	ttccctattc	atacgttact	180
tggtctctct	catattcctt	gagtgtttta	aattgtaaac	attcaagtac	aaacaaactt	240
cgcttgatta	ccagagataa	aaaagaaatg	ccttgtaatt	tggtgtcatg	tgaatgtttt	300
aagtggatac	ctgaaaaaatt	gtacttaaga	atggcataa			339

<210> 31

<211> 112
 <212> PRT
 <213> Homo Sapiens

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 Phe Asp Arg Glu Gly Arg Arg Arg Glu Gln Asn Ser Thr His Ser Ser
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 Asn Asn Leu Ile Ala Ser Cys Glu Gln Ala Lys Arg Met Phe Ile Val
 35 40 45
 Ser Leu Ile Gly Ala Ile Pro Tyr Ser Tyr Val Thr Cys Ala Leu Ser
 50 55 60
 Tyr Ser Leu Ser Val Leu Asn Cys Lys His Ser Ser Thr Asn Lys Leu
 65 70 75 80
 Arg Leu Ile Thr Arg Asp Lys Lys Glu Met Pro Cys Asn Leu Val Ser
 85 90 95
 Cys Glu Cys Phe Lys Trp Ile Pro Glu Lys Leu Tyr Leu Arg Met Ala
 100 105 110

<210> 32
 <211> 63
 <212> DNA
 <213> Homo Sapiens

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 taa 63

<210> 33
 <211> 20
 <212> PRT
 <213> Homo Sapiens

<400> 33
 Met Asn Leu Thr Gly Arg Val Glu Gly Glu Asn Arg Ile Gln Pro Thr
 1 5 10 15
 Ala Ala Thr Ile
 20

<210> 34
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 <212> DNA
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 tattccttga gtgttttaaa ttgtaaacat tcaagtacaa acaaacttcg ctgattacc 120
 agagataaaa aagaaatgcc ttgtaatttg gtgtcatgtg aatgttttaa gtggatacct 180
 gaaaaattgt acttaagaat ggcataa 207

<210> 35
 <211> 68
 <212> PRT
 <213> Homo Sapiens

<400> 35
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 1 5 10 15
 Cys Ala Leu Ser Tyr Ser Leu Ser Val Leu Asn Cys Lys His Ser Ser
 20 25 30
 Thr Asn Lys Leu Arg Leu Ile Thr Arg Asp Lys Lys Glu Met Pro Cys
 35 40 45
 Asn Leu Val Ser Cys Glu Cys Phe Lys Trp Ile Pro Glu Lys Leu Tyr
 50 55 60

Leu Arg Met Ala
65

<210> 36
<211> 72
<212> DNA
<213> Homo Sapiens

<400> 36
atgccttgta atttgggtgc atgtgaatgt tttaagtgga tacctgaaaa attgtactta 60
agaatggcat aa 72

<210> 37
<211> 23
<212> PRT
<213> Homo Sapiens

<400> 37
Met Pro Cys Asn Leu Val Ser Cys Glu Cys Phe Lys Trp Ile Pro Glu
1 5 10 15
Lys Leu Tyr Leu Arg Met Ala
20

<210> 38
<211> 24
<212> DNA
<213> Homo Sapiens

<400> 38
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<210> 39
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<213> Homo Sapiens

<400> 39
Met His Arg Leu Ser Ile His
1 5

<210> 40
<211> 21
<212> DNA
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<400> 41
Met Gly Pro Leu Pro Ser
1 5

<210> 42
<211> 36
<212> DNA
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 <212> PRT
 <213> Homo Sapiens

<400> 43
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 1 5 10

<210> 44
 <211> 183
 <212> DNA
 <213> Homo Sapiens

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 35 40 45
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 50 55 60

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<210> 63

<211> 12
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<210> 75
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 <212> DNA
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<400> 76
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<211> 93
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 gcctgtttac caaaaacatc acctctagca tcaccagtat tagaggcacc gcctgccag 180
 tgacacatgt ttaacggcgc cggtagcccta accgtgcaaa ggtagcataa tcacttgttc 240

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<210> 86

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<213> Homo Sapiens

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<211> 15

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<213> Homo Sapiens

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<210> 92
<211> 99
<212> DNA
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aacaaccca caggctcctaa actaccaaac ctgcattaa 99

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<211> 32
<212> PRT
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<400> 93
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<210> 97

<211> 17
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<400> 97
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<210> 98
<211> 45
<212> DNA
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<400> 98
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<211> 63
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<210> 101
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<400> 101
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<210> 102
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<400> 103
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<210> 104

<211> 116
 <212> DNA
 <213> Homo Sapiens

<400> 104
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 <211> 38
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<400> 105
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 Tyr Ser Leu Lys Ile Glu Cys Gly Pro Lys Tyr Pro Glu Ala Pro Pro
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 85 90 95
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 100 105 110
 Asn Ser Tyr Ser Ile Lys Val Val Leu Gln Glu Leu Arg Arg Leu Met
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<210> 111
 <211> 15
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<210> 112
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<400> 112
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 <211> 318
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 agatttgtaa caaaaattaa tatgaatgga gtaaatagtt ctaatggagt ggtggaccca 180
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 <212> PRT
 <213> Homo Sapiens

<400> 114
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 35 40 45
 Asn Gly Val Asn Ser Ser Asn Gly Val Val Asp Pro Arg Ala Ile Ser
 50 55 60
 Val Leu Ala Lys Trp Gln Asn Ser Tyr Ser Ile Lys Val Val Leu Gln
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 <211> 42
 <212> DNA
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<400> 115
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<210> 116
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 <212> PRT
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<400> 116
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<210> 117
 <211> 294
 <212> DNA
 <213> Homo Sapiens

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tggcagaatt catatagcat caaagttgtc ctgcaagagc ttcggcgcct aatgatgtct 240
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<211> 97

<212> PRT

<213> Homo Sapiens

<400> 118

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		20					25						30		
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	35					40					45				
Val	Val	Asp	Pro	Arg	Ala	Ile	Ser	Val	Leu	Ala	Lys	Trp	Gln	Asn	Ser
	50				55					60					
Tyr	Ser	Ile	Lys	Val	Val	Leu	Gln	Glu	Leu	Arg	Arg	Leu	Met	Met	Ser
65				70				75						80	
Lys	Glu	Asn	Met	Lys	Leu	Pro	Gln	Pro	Pro	Glu	Gly	Gln	Cys	Tyr	Ser
			85					90						95	

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<210> 119

<211> 30

<212> DNA

<213> Homo Sapiens

<400> 119

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30

<210> 120

<211> 9

<212> PRT

<213> Homo Sapiens

<400> 120

Met Lys Thr Glu Tyr Thr Ala Leu Lys
1 5

<210> 121

<211> 12

<212> DNA

<213> Homo Sapiens

<400> 121

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12

<210> 122

<211> 3

<212> PRT

<213> Homo Sapiens

<400> 122

Met Trp Thr
1

<210> 123

<211> 177

<212> DNA

<213> Homo Sapiens

<400> 123

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atgaatggag taaatagttc taatggagtg gtggacccaa gagccatatt agtgctagca      60
aaatggcaga attcatatag catcaaagtt gtcttgcaag agcttcggcg cctaattgatg      120
tctaaagaaa atatgaaact ccctcagccg cccgaaggac agtgttacag caattaa      177

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<210> 124

<211> 58

<212> PRT

<213> Homo Sapiens

<400> 124

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Ser Val Leu Ala Lys Trp Gln Asn Ser Tyr Ser Ile Lys Val Val Leu
      20              25              30
Gln Glu Leu Arg Arg Leu Met Met Ser Lys Glu Asn Met Lys Leu Pro
      35              40              45
Gln Pro Pro Glu Gly Gln Cys Tyr Ser Asn
      50              55

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<210> 125

<211> 36

<212> DNA

<213> Homo Sapiens

<400> 125

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atggagtggg ggacccaaga gccatatcag tgctag      36

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<210> 126

<211> 11

<212> PRT

<213> Homo Sapiens

<400> 126

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  1              5              10

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<210> 127

<211> 18

<212> DNA

<213> Homo Sapiens

<400> 127

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<210> 128

<211> 5

<212> PRT

<213> Homo Sapiens

<400> 128

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Met Ala Glu Phe Ile
  1              5

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<210> 129

<211> 63

<212> DNA

<213> Homo Sapiens

<400> 129

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taa      63

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<212> PRT
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<400> 130
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1 5 10 15
Cys Tyr Ser Asn
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<210> 131
<211> 60
<212> DNA
<213> Homo Sapiens

<400> 131
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<210> 132
<211> 19
<212> PRT
<213> Homo Sapiens

<400> 132
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1 5 10 15
Tyr Ser Asn

<210> 133
<211> 45
<212> DNA
<213> Homo Sapiens

<400> 133
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<210> 134
<211> 14
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<400> 134
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1 5 10

<210> 135
<211> 27
<212> DNA
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<400> 135
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<210> 136
<211> 8
<212> PRT
<213> Homo Sapiens

<400> 136
Met Ile Leu Ile Phe Ser Ser Ile
1 5

<210> 137

<211> 72
<212> DNA
<213> Homo Sapiens

<400> 137
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catagattgt aa 72

<210> 138
<211> 23
<212> PRT
<213> Homo Sapiens

<400> 138
Met Pro Leu Pro Asn His His Pro Val Pro Thr Leu Leu His Ser Arg
1 5 10 15
Pro Trp Pro Lys His Arg Leu
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<210> 139
<211> 57
<212> DNA
<213> Homo Sapiens

<400> 139
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<210> 140
<211> 18
<212> PRT
<213> Homo Sapiens

<400> 140
Met Thr Leu Pro Cys Phe Gly Gln Lys Pro Ser Gly Lys Val Gly Lys
1 5 10 15
Ser Leu

<210> 141
<211> 48
<212> DNA
<213> Homo Sapiens

<400> 141
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<210> 142
<211> 15
<212> PRT
<213> Homo Sapiens

<400> 142
Met Asn Ile Gly Ser Ser Ala Leu Pro Pro Ser Ala Val Ile Ser
1 5 10 15

<210> 143
<211> 15
<212> DNA
<213> Homo Sapiens

<400> 143
atgcattggt ttttag 15

<210> 144
<211> 4

<212> PRT

<213> Homo Sapiens

<400> 144

Met His Cys Phe

1

<210> 145

<211> 78

<212> DNA

<213> Homo Sapiens

<400> 145

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tttgctttta aaaattga

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78

<210> 146

<211> 25

<212> PRT

<213> Homo Sapiens

<400> 146

Met Lys Ile Leu Val Ser Thr His Asp Pro Ser Glu Leu Phe Tyr Phe
1 5 10 15
Pro Val Thr Ala Phe Ala Phe Lys Asn
20 25

<210> 147

<211> 33

<212> DNA

<213> Homo Sapiens

<400> 147

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33

<210> 148

<211> 10

<212> PRT

<213> Homo Sapiens

<400> 148

Met Ile Pro Leu Asn Cys Phe Thr Phe Leu
1 5 10

<210> 149

<211> 156

<212> DNA

<213> Homo Sapiens

<400> 149

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cccgggtgtgc acagcagatc cccgaaattg gtgggcttga cctcctggca aattgctgctg
tctttccact tgctgttcag gaccactaaa tgctga

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120

156

<210> 150

<211> 51

<212> PRT

<213> Homo Sapiens

<400> 150

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1 5 10 15
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20 25 30
Leu Thr Ser Trp Gln Ile Ala Ala Ser Phe His Leu Leu Phe Arg Thr

35
Thr Lys Cys
50

40

45

<210> 151
<211> 30
<212> DNA
<213> Homo Sapiens

<400> 151
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30

<210> 152
<211> 9
<212> PRT
<213> Homo Sapiens

<400> 152
Met Leu Lys Cys Gly Cys Ile Pro Lys
1 5

<210> 153
<211> 69
<212> DNA
<213> Homo Sapiens

<400> 153
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ttaatttag

60

69

<210> 154
<211> 22
<212> PRT
<213> Homo Sapiens

<400> 154
Met Trp Met His Thr Glu Ile Lys Ala Ile His Cys Val Leu Lys Val
1 5 10 15
Phe Phe Phe Phe Leu Ile
20

<210> 155
<211> 63
<212> DNA
<213> Homo Sapiens

<400> 155
atgcataccg aaataaaaagc aattcattgt gtactaaagg tttttttttt ttttttaatt
tag

60

63

<210> 156
<211> 20
<212> PRT
<213> Homo Sapiens

<400> 156
Met His Thr Glu Ile Lys Ala Ile His Cys Val Leu Lys Val Phe Phe
1 5 10 15
Phe Phe Leu Ile
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<210> 157
<211> 66
<212> DNA
<213> Homo Sapiens

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<210> 158
 <211> 21
 <212> PRT
 <213> Homo Sapiens

<400> 158
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 1 5 10 15
 Leu Thr Ser Cys Lys
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<210> 159
 <211> 1293
 <212> DNA
 <213> Homo Sapiens

<400> 159
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 aataaaataa aatatatact atcttgctcc tcagaaccag tggggaagaa gagggaaggc 180
 aaagaaagaa actgagcata gtaaacacag catttttttg taggctctta tttaaaatgt 240
 gtgtgtgtgt gtgtatgtgt gtgtttctga gtaagtattg actgggaaaa agagagaagt 300
 caatcaaaag tatactgtgc aattgagaga ggctggccca agatttaaaa ctccctgtgg 360
 gtaatctaac tgtgagtaga taggaatcgg ccatatgacg aaatgagatc aataggaaat 420
 gtgctttttg aggaaatttt attttagtac caaatgttgc cagtgcacat cttcagttaa 480
 gaagtaagtt atttgaccta aaattcttat ctctgccact ttggttttaa aacaaaaacc 540
 cttatataca tggaaatagtt atattttaat taagcattta ttttagttgt tttcatccat 600
 tcaagcaaaa tgaataagca gcatttttca ttgcacttaa aaatgtaaaa tacctgcatg 660
 ccactaatct gtaacatttt accagttcag atgcctgtaa tgtgtgactt tatgtgtgtc 720
 tgtgttgttt tgaagagaat aaaggaaata atactttgca aactgtttaa acaagtgttt 780
 aaacttctat tggcaacatt tattgggcta agcagttatt gaaaactccg catagtttta 840
 ttttccattt gaaacttcaa tcaaatcaag actattatat tcattagggg attaaagact 900
 aatttgcttt ttaaatgtga agtggaaacac tgtgtggaaa gtaaatgtgt gatgaagcaa 960
 aatgtataaa gtatgaaata ttatactttt accctggata attattcagg accccagttg 1020
 gcccaaataa gtgcaatttt taatcctttg aaattagcca gccagaccta atgctaaggt 1080
 aaatgtaaac tgttttaatt aattaagatc tttctgcttt cgaaggata atgtatctat 1140
 ttctgtcagg aatgatattt ccaaatgaaa atgtaaagaa cattgggaaa taataaactt 1200
 tcctttcaaa gtaaaagtaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1260
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<210> 160
 <211> 45
 <212> DNA
 <213> Homo Sapiens

<400> 160
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<210> 161
 <211> 14
 <212> PRT
 <213> Homo Sapiens

<400> 161
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 1 5 10

<210> 162
 <211> 27
 <212> DNA
 <213> Homo Sapiens

<400> 162
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<210> 163
<211> 8
<212> PRT
<213> Homo Sapiens

<400> 163
Met Cys Val Phe Leu Ser Lys Tyr
1 5

<210> 164
<211> 12
<212> DNA
<213> Homo Sapiens

<400> 164
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<210> 165
<211> 3
<212> PRT
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<400> 165
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<210> 166
<211> 45
<212> DNA
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<400> 166
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<210> 167
<211> 14
<212> PRT
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<400> 167
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1 5 10

<210> 168
<211> 48
<212> DNA
<213> Homo Sapiens

<400> 168
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<210> 169
<211> 15
<212> PRT
<213> Homo Sapiens

<400> 169
Met Cys Phe Leu Arg Lys Phe Tyr Phe Ser Thr Lys Cys Cys Gln
1 5 10 15

<210> 170
<211> 27

<212> DNA
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<400> 170
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27

<210> 171
<211> 8
<212> PRT
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<400> 171
Met Leu Pro Val Thr Ile Phe Ser
1 5

<210> 172
<211> 39
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39

<210> 173
<211> 12
<212> PRT
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<400> 173
Met Asn Lys Gln His Phe Ser Leu His Leu Lys Met
1 5 10

<210> 174
<211> 165
<212> DNA
<213> Homo Sapiens

<400> 174
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gtctgtgttg ttttgaagag aataaaggaa ataatacttt gcaaactgtt taaacaagtg 120
tttaaacttc tattggcaac atttattggg ctaagcagtt attga 165

<210> 175
<211> 54
<212> PRT
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<400> 175
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1 5 10 15
Asp Phe Met Cys Val Cys Val Val Leu Lys Arg Ile Lys Glu Ile Ile
20 25 30
Leu Cys Lys Leu Phe Lys Gln Val Phe Lys Leu Leu Leu Ala Thr Phe
35 40 45
Ile Gly Leu Ser Ser Tyr
50

<210> 176
<211> 132
<212> DNA
<213> Homo Sapiens

<400> 176
atgcctgtaa tgtgtgactt tatgtgtgtc tgtgttgttt tgaagagaat aaaggaaata 60
atactttgca aactgtttta acaagtgttt aaacttctat tggcaacatt tattgggcta 120

agcagttatt ga

132

<210> 177

<211> 43

<212> PRT

<213> Homo Sapiens

<400> 177

Met	Pro	Val	Met	Cys	Asp	Phe	Met	Cys	Val	Cys	Val	Val	Leu	Lys	Arg
1				5					10					15	
Ile	Lys	Glu	Ile	Ile	Leu	Cys	Lys	Leu	Phe	Lys	Gln	Val	Phe	Lys	Leu
			20					25					30		
Leu	Leu	Ala	Thr	Phe	Ile	Gly	Leu	Ser	Ser	Tyr					
		35					40								

<210> 178

<211> 123

<212> DNA

<213> Homo Sapiens

<400> 178

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aaactgttta	aacaagtgtt	taaacttcta	ttggcaacat	ttattgggct	aagcagttat	120
tga						123

<210> 179

<211> 40

<212> PRT

<213> Homo Sapiens

<400> 179

Met	Cys	Asp	Phe	Met	Cys	Val	Cys	Val	Val	Leu	Lys	Arg	Ile	Lys	Glu
1				5					10					15	
Ile	Ile	Leu	Cys	Lys	Leu	Phe	Lys	Gln	Val	Phe	Lys	Leu	Leu	Leu	Ala
			20					25					30		
Thr	Phe	Ile	Gly	Leu	Ser	Ser	Tyr								
		35					40								

<210> 180

<211> 111

<212> DNA

<213> Homo Sapiens

<400> 180

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caagtgttta	aacttctatt	ggcaacattt	attgggctaa	gcagttattg	a	111

<210> 181

<211> 36

<212> PRT

<213> Homo Sapiens

<400> 181

Met	Cys	Val	Cys	Val	Val	Leu	Lys	Arg	Ile	Lys	Glu	Ile	Ile	Leu	Cys
1				5					10					15	
Lys	Leu	Phe	Lys	Gln	Val	Phe	Lys	Leu	Leu	Leu	Ala	Thr	Phe	Ile	Gly
			20					25					30		
Leu	Ser	Ser	Tyr												
		35													

<210> 182

<211> 57

<212> DNA

<213> Homo Sapiens

<400> 182
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<210> 183
<211> 18
<212> PRT
<213> Homo Sapiens

<400> 183
Met Cys Asp Glu Ala Lys Cys Ile Lys Tyr Glu Ile Leu Tyr Phe Tyr
1 5 10 15
Pro Gly

<210> 184
<211> 18
<212> DNA
<213> Homo Sapiens

<400> 184
atgaagcaaa atgtataa 18

<210> 185
<211> 5
<212> PRT
<213> Homo Sapiens

<400> 185
Met Lys Gln Asn Val
1 5

<210> 186
<211> 15
<212> DNA
<213> Homo Sapiens

<400> 186
atgtataaag tatga 15

<210> 187
<211> 4
<212> PRT
<213> Homo Sapiens

<400> 187
Met Tyr Lys Val
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<210> 188
<211> 99
<212> DNA
<213> Homo Sapiens

<400> 188
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gcaattttta atcctttgaa attagccagc cagacctaa 99

<210> 189
<211> 32
<212> PRT
<213> Homo Sapiens

<400> 189
Met Lys Tyr Tyr Thr Phe Thr Leu Asp Asn Tyr Ser Gly Pro Gln Leu
1 5 10 15

Ala Gln Ile Gly Ala Ile Phe Asn Pro Leu Lys Leu Ala Ser Gln Thr
20 25 30

<210> 190
<211> 12
<212> DNA
<213> Homo Sapiens

<400> 190
atgctaagggt aa

12

<210> 191
<211> 3
<212> PRT
<213> Homo Sapiens

<400> 191
Met Leu Arg
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<210> 192
<211> 63
<212> DNA
<213> Homo Sapiens

<400> 192
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taa

60
63

<210> 193
<211> 20
<212> PRT
<213> Homo Sapiens

<400> 193
Met Tyr Leu Phe Leu Ser Gly Met Ile Phe Pro Asn Glu Asn Val Lys
1 5 10 15
Asn Ile Gly Lys
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<210> 194
<211> 42
<212> DNA
<213> Homo Sapiens

<400> 194
atgatatttc caaatgaaaa tgtaaagaac attgggaaat aa

42

<210> 195
<211> 13
<212> PRT
<213> Homo Sapiens

<400> 195
Met Ile Phe Pro Asn Glu Asn Val Lys Asn Ile Gly Lys
1 5 10

<210> 196
<211> 12
<212> DNA
<213> Homo Sapiens

<400> 196
atgaaaatgt aa

12

<210> 197
 <211> 3
 <212> PRT
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<400> 197
 Met Lys Met
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<210> 198
 <211> 1466
 <212> DNA
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 ttttgggtgt tagactgaaa ttttttaaga gtatttaacc tttccagtat tctgtttcac 180
 gcttagatgg aaatgtatct tatgaataga gacatattaa aataatgttt acatcttaga 240
 aaaaacatag atagtgcctag taatattact tataactgta atatatagat tcagaaatac 300
 attttcatta tccaaaatca gcttcaacaa atgggttctg gagacaaata atttgttttc 360
 attatcattg tataatcagg ttaatgattt attttttgac taaatgtgca atttcttctc 420
 actagataac tttcagtatc agtgggtggtt acttattact taaatcagag gaaggatttt 480
 ataaagatta ataaatttaa ttttaccat aaatatccc ataatttaga aaaggatgtc 540
 gacttgctaa tttcagaaat aattattcat ttttaaaaag ccccttttaa agcatctact 600
 tgaagattgg tataattttc ataaaatgtc ttttttttta gtgtcccaa gatattcttag 660
 ataaactatt ttgaagttca gatttcagat gaggcaacat tttcttgaga taattaccca 720
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 agataactag gataacttgt tgctttgtta cccagcctaa ttgaagagtg gcagagacta 840
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 gtctttacaa tgcttggttc aaagaaccaa cagaaaaaaa agctaagaaa actgagaact 960
 aacattaaaa aaattaaatt tagaataaga atgatttctt taatttgtcc tttttttctt 1020
 tgggtctaaa cattattaaa tttttgtaa tattttgatt taatgtgtct tagatcctca 1080
 ttattttaat acaggaaaag aaaagattta gtaatttctt accatgctaa tatgtaaagt 1140
 tcatgccatc caggcattta agagcgatcc tcatcccttc agcaatatgt atttgagttc 1200
 acactatttc tgttttacag cagttttgaa aaacacatac tatgccacca attgtcatat 1260
 tatttttaga tgatgtaaca tagccatcaa aattaatatt atgtaatgcc taatacttag 1320
 tatgtaaatg tcacgagatc atttttacat taaacgtgaa aaaaaatcaa aaaaaaaaaa 1380
 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1440
 aaaaaaaaaa aaaaaaaagg gcggcc 1466

<210> 199
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 <212> DNA
 <213> Homo Sapiens

<400> 199
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 agtattttaa 129

<210> 200
 <211> 42
 <212> PRT
 <213> Homo Sapiens

<400> 200
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 1 5 10 15
 Asp Ile Leu Trp Ile Pro Pro Leu His Trp Gln Asn Thr Met Leu Leu
 20 25 30
 Gly Val Arg Leu Lys Tyr Phe Lys Ser Ile
 35 40

<210> 201

<211> 69
<212> DNA
<213> Homo Sapiens

<400> 201
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ttagactga 69

<210> 202
<211> 22
<212> PRT
<213> Homo Sapiens

<400> 202
Met Cys Leu Ile Phe Cys Gly Tyr Leu Pro Cys Thr Gly Lys Thr Leu
1 5 10 15
Cys Phe Trp Val Leu Asp
20

<210> 203
<211> 42
<212> DNA
<213> Homo Sapiens

<400> 203
atgcttttgg gtgtagact gaaatatttt aagagtattt aa 42

<210> 204
<211> 13
<212> PRT
<213> Homo Sapiens

<400> 204
Met Leu Leu Gly Val Arg Leu Lys Tyr Phe Lys Ser Ile
1 5 10

<210> 205
<211> 39
<212> DNA
<213> Homo Sapiens

<400> 205
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<210> 206
<211> 12
<212> PRT
<213> Homo Sapiens

<400> 206
Met Glu Met Tyr Leu Met Asn Arg Asp Ile Leu Lys
1 5 10

<210> 207
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42

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1 5 10

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<210> 225
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 Ser Asp Asn

<210> 227
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 <212> DNA
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 acattattaa atttttgtaa atattttgat ttaatgtgtc ttagatcctc attattttaa 180

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<400> 230
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 Thr Asn Ile Lys Lys Ile Lys Phe Arg Ile Arg Met Ile Ser Leu Ile
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 Cys Pro Phe Phe Leu Trp Ser Lys Thr Leu Leu Asn Phe Cys Lys Tyr
 35 40 45
 Phe Asp Leu Met Cys Leu Arg Ser Ser Leu Phe
 50 55

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 <212> DNA
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 <211> 32
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<400> 232
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 20 25 30

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<400> 233
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<210> 234
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<400> 234
 Met Cys Leu Arg Ser Ser Leu Phe
 1 5

<210> 235
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<210> 236
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<213> Homo Sapiens

<400> 236

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Met Leu Ile Cys Lys Val His Ala Ile Gln Ala Phe Lys Ser Asp Pro
 1             5             10             15
His Pro Phe Ser Asn Met Tyr Leu Ser Ser His Tyr Phe Cys Phe Thr
      20             25             30
Ala Val Leu Lys Asn Thr Tyr Tyr Ala Thr Asn Cys His Ile Ile Phe
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Arg

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<210> 237

<211> 54

<212> DNA

<213> Homo Sapiens

<400> 237

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<211> 17

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<213> Homo Sapiens

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Met Pro Ser Arg His Leu Arg Ala Ile Leu Ile Pro Ser Ala Ile Cys
 1             5             10             15
Ile

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<210> 239

<211> 87

<212> DNA

<213> Homo Sapiens

<400> 239

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60
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<210> 240

<211> 28

<212> PRT

<213> Homo Sapiens

<400> 240

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<211> 42

<212> DNA

<213> Homo Sapiens

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<211> 13

<212> PRT

<213> Homo Sapiens

<400> 242

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 1 5 10

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<400> 243
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<210> 244
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<210> 245
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 aaaaaaaaaa agggcggcc 139

<210> 246
 <211> 46
 <212> PRT
 <213> Homo Sapiens

<400> 246
 Met Ser Arg Asp His Phe Tyr Ile Lys Arg Glu Lys Lys Ser Lys Lys
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 20 25 30
 Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Gly Gly
 35 40 45

<210> 247
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 <212> DNA
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<400> 247
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<210> 248

<211> 1386

<212> DNA

<213> Homo Sapiens

<400> 248

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<211> 461

<212> PRT

<213> Homo Sapiens

<400> 249

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20          25          30
Thr Thr Trp Asp Ser Gly Phe Cys Ala Val Asn Pro Lys Phe Val Ala
35          40          45
Leu Ile Cys Glu Ala Ser Gly Gly Gly Ala Phe Leu Val Leu Pro Leu
50          55          60
Gly Lys Thr Gly Arg Val Asp Lys Asn Ala Pro Thr Val Cys Gly His
65          70          75          80
Thr Ala Pro Val Leu Asp Ile Ala Trp Cys Pro His Asn Asp Asn Val
85          90          95
Ile Ala Ser Gly Ser Glu Asp Cys Thr Val Met Val Trp Glu Ile Pro
100         105         110
Asp Gly Gly Leu Met Leu Pro Leu Arg Glu Pro Val Val Thr Leu Glu

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115 120 125
 Gly His Thr Lys Arg Val Gly Ile Val Ala Trp His Thr Thr Ala Gln
 130 135 140
 Asn Val Leu Leu Ser Ala Gly Cys Asp Asn Val Ile Met Val Trp Asp
 145 150 155 160
 Val Gly Thr Gly Ala Ala Met Leu Thr Leu Gly Pro Glu Val His Pro
 165 170 175
 Asp Thr Ile Tyr Ser Val Asp Trp Ser Arg Asp Gly Gly Leu Ile Cys
 180 185 190
 Thr Ser Cys Arg Asp Lys Arg Val Arg Ile Ile Glu Pro Arg Lys Gly
 195 200 205
 Thr Val Val Ala Glu Lys Asp Arg Pro His Glu Gly Thr Arg Pro Val
 210 215 220
 Arg Ala Val Phe Val Ser Glu Gly Lys Ile Leu Thr Thr Gly Phe Ser
 225 230 235 240
 Arg Met Ser Glu Arg Gln Val Ala Leu Trp Asp Thr Lys His Leu Glu
 245 250 255
 Glu Pro Leu Ser Leu Gln Glu Leu Asp Thr Ser Ser Gly Val Leu Leu
 260 265 270
 Pro Phe Phe Asp Pro Asp Thr Asn Ile Val Tyr Leu Cys Gly Lys Gly
 275 280 285
 Asp Ser Ser Ile Arg Tyr Phe Glu Ile Thr Ser Glu Ala Pro Phe Leu
 290 295 300
 His Tyr Leu Ser Met Phe Ser Ser Lys Glu Ser Gln Arg Gly Met Gly
 305 310 315 320
 Tyr Met Pro Lys Arg Gly Leu Glu Val Asn Lys Cys Glu Ile Ala Arg
 325 330 335
 Phe Tyr Lys Leu His Glu Arg Arg Cys Glu Pro Ile Ala Met Thr Val
 340 345 350
 Pro Arg Lys Ser Asp Leu Phe Gln Glu Asp Leu Tyr Pro Pro Thr Ala
 355 360 365
 Gly Pro Asp Pro Ala Leu Thr Ala Glu Glu Trp Leu Gly Gly Arg Asp
 370 375 380
 Ala Gly Pro Leu Leu Ile Ser Leu Lys Asp Gly Tyr Val Pro Pro Lys
 385 390 395 400
 Ser Arg Glu Leu Arg Val Asn Arg Gly Leu Asp Thr Gly Arg Arg Arg
 405 410 415
 Ala Ala Pro Glu Ala Ser Gly Thr Pro Ser Ser Asp Ala Val Ser Arg
 420 425 430
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<210> 250

<211> 75

<212> DNA

<213> Homo Sapiens

<400> 250

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<210> 251

<211> 24

<212> PRT

<213> Homo Sapiens

<400> 251

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<210> 252

<211> 69
 <212> DNA
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<400> 252
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<210> 253
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 <212> PRT
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<400> 253
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 1 5 10 15
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<210> 254
 <211> 39
 <212> DNA
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<400> 254
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<210> 255
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<210> 256
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<210> 257
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<400> 257
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<210> 258
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<210> 259

<211> 355

<212> PRT

<213> Homo Sapiens

<400> 259

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Pro	Val	Val	Thr	Leu	Glu	Gly	His	Thr	Lys	Arg	Val	Gly	Ile	Val	Ala
			20					25					30		
Trp	His	Thr	Thr	Ala	Gln	Asn	Val	Leu	Leu	Ser	Ala	Gly	Cys	Asp	Asn
			35				40					45			
Val	Ile	Met	Val	Trp	Asp	Val	Gly	Thr	Gly	Ala	Ala	Met	Leu	Thr	Leu
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Gly	Pro	Glu	Val	His	Pro	Asp	Thr	Ile	Tyr	Ser	Val	Asp	Trp	Ser	Arg
65					70				75					80	
Asp	Gly	Gly	Leu	Ile	Cys	Thr	Ser	Cys	Arg	Asp	Lys	Arg	Val	Arg	Ile
				85					90					95	
Ile	Glu	Pro	Arg	Lys	Gly	Thr	Val	Val	Ala	Glu	Lys	Asp	Arg	Pro	His
			100					105					110		
Glu	Gly	Thr	Arg	Pro	Val	Arg	Ala	Val	Phe	Val	Ser	Glu	Gly	Lys	Ile
			115				120					125			
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145					150					155				160	
Ser	Ser	Gly	Val	Leu	Leu	Pro	Phe	Phe	Asp	Pro	Asp	Thr	Asn	Ile	Val
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Ser	Glu	Ala	Pro	Phe	Leu	His	Tyr	Leu	Ser	Met	Phe	Ser	Ser	Lys	Glu
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Ser	Gln	Arg	Gly	Met	Gly	Tyr	Met	Pro	Lys	Arg	Gly	Leu	Glu	Val	Asn
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225					230					235				240	
Pro	Ile	Ala	Met	Thr	Val	Pro	Arg	Lys	Ser	Asp	Leu	Phe	Gln	Glu	Asp
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Leu	Tyr	Pro	Pro	Thr	Ala	Gly	Pro	Asp	Pro	Ala	Leu	Thr	Ala	Glu	Glu
	260					265							270		
Trp	Leu	Gly	Gly	Arg	Asp	Ala	Gly	Pro	Leu	Leu	Ile	Ser	Leu	Lys	Asp
	275						280					285			
Gly	Tyr	Val	Pro	Pro	Lys	Ser	Arg	Glu	Leu	Arg	Val	Asn	Arg	Gly	Leu
	290					295					300				
Asp	Thr	Gly	Arg	Arg	Arg	Ala	Ala	Pro	Glu	Ala	Ser	Gly	Thr	Pro	Ser
305					310					315				320	
Ser	Asp	Ala	Val	Ser	Arg	Leu	Glu	Glu	Glu	Met	Arg	Lys	Leu	Gln	Ala
				325					330					335	
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355

<210> 260
<211> 12
<212> DNA
<213> Homo Sapiens

345

350

<400> 260
atgggggcct ga

12

<210> 261
<211> 3
<212> PRT
<213> Homo Sapiens

<400> 261
Met Gly Ala
1

<210> 262
<211> 1038
<212> DNA
<213> Homo Sapiens

<400> 262
atgctgcccc tgcgggagcc cgtcgtcacc ctggagggcc acaccaagcg tgtgggcatt 60
gtggcctggc acaccacagc ccagaacgtg ctgctcagtg cagggttgta caacgtgatc 120
atggtgtggg acgtgggcac tggggcggcc atgctgacac tgggcccaga ggtgcaccca 180
gacacgatct acagtgtgga ctggagccga gatggaggcc tcatttgtag ctctgcccgt 240
gacaagcgcg tgcgcatcat cgagcccccgc aaaggcactg tcgtagctga gaaggaccgt 300
ccccacgagg ggacccggcc cgtgctgtga gtgttcgtgt cggaggggaa gatcctgacc 360
acgggcttca gccgcatgag tgagcggcag gtggcgctgt gggacacaaa gcacctggag 420
gagccgctgt cctgagcagga gctggacacc agcagcgggtg tcctgctgcc cttctttgac 480
cctgacacca acatcgtcta cctctgtggc aaggggtgaca gctcaatccg gtactttgag 540
atcacttccg agggcccttt cctgcactat ctctccatgt tcagttccaa ggagtcccag 600
cggggcatgg gctacatgcc caaacgtggc ctggaggtga acaagtgtga gatcgccagg 660
ttctacaagc tgcacgagcg gaggtgtgag cccattgccg tgacagtgcc tcgaaagtccg 720
gacctgttcc agggaggacct gtacccaccc accgcagggc cgcaccctgc cctcacggct 780
gaggagtggc tgggggggtcg ggatgctggg cccctcctca tctccctcaa ggatggctac 840
gtacccccaa agagccggga gctgagggtc aaccggggcc tggacaccgg gcgcaggagg 900
gcagcaccag aggccagtgg cactcccagc tcggatgccg tgtctcggct ggaggaggag 960
atgcggaagc tccaggccac ggtgcaggag ctccagaagc gcttggacag gctggaggag 1020
acagtccagg ccaagtag 1038

<210> 263
<211> 345
<212> PRT
<213> Homo Sapiens

<400> 263
Met Leu Pro Leu Arg Glu Pro Val Val Thr Leu Glu Gly His Thr Lys
1 5 10 15
Arg Val Gly Ile Val Ala Trp His Thr Ala Gln Asn Val Leu Leu
20 25 30
Ser Ala Gly Cys Asp Asn Val Ile Met Val Trp Asp Val Gly Thr Gly
35 40 45
Ala Ala Met Leu Thr Leu Gly Pro Glu Val His Pro Asp Thr Ile Tyr
50 55 60
Ser Val Asp Trp Ser Arg Asp Gly Gly Leu Ile Cys Thr Ser Cys Arg
65 70 75 80
Asp Lys Arg Val Arg Ile Ile Glu Pro Arg Lys Gly Thr Val Val Ala
85 90 95
Glu Lys Asp Arg Pro His Glu Gly Thr Arg Pro Val Arg Ala Val Phe

45

100 105 110
 Val Ser Glu Gly Lys Ile Leu Thr Thr Gly Phe Ser Arg Met Ser Glu
 115 120 125
 Arg Gln Val Ala Leu Trp Asp Thr Lys His Leu Glu Glu Pro Leu Ser
 130 135 140
 Leu Gln Glu Leu Asp Thr Ser Ser Gly Val Leu Leu Pro Phe Phe Asp
 145 150 155 160
 Pro Asp Thr Asn Ile Val Tyr Leu Cys Gly Lys Gly Asp Ser Ser Ile
 165 170 175
 Arg Tyr Phe Glu Ile Thr Ser Glu Ala Pro Phe Leu His Tyr Leu Ser
 180 185 190
 Met Phe Ser Ser Lys Glu Ser Gln Arg Gly Met Gly Tyr Met Pro Lys
 195 200 205
 Arg Gly Leu Glu Val Asn Lys Cys Glu Ile Ala Arg Phe Tyr Lys Leu
 210 215 220
 His Glu Arg Arg Cys Glu Pro Ile Ala Met Thr Val Pro Arg Lys Ser
 225 230 235 240
 Asp Leu Phe Gln Glu Asp Leu Tyr Pro Pro Thr Ala Gly Pro Asp Pro
 245 250 255
 Ala Leu Thr Ala Glu Glu Trp Leu Gly Gly Arg Asp Ala Gly Pro Leu
 260 265 270
 Leu Ile Ser Leu Lys Asp Gly Tyr Val Pro Pro Lys Ser Arg Glu Leu
 275 280 285
 Arg Val Asn Arg Gly Leu Asp Thr Gly Arg Arg Arg Ala Ala Pro Glu
 290 295 300
 Ala Ser Gly Thr Pro Ser Ser Asp Ala Val Ser Arg Leu Glu Glu Glu
 305 310 315 320
 Met Arg Lys Leu Gln Ala Thr Val Gln Glu Leu Gln Lys Arg Leu Asp
 325 330 335
 Arg Leu Glu Glu Thr Val Gln Ala Lys
 340 345

<210> 264

<211> 918

<212> DNA

<213> Homo Sapiens

<400> 264

atggtgtggg	acgtgggcac	tggggcggcc	atgctgacac	tggggcccaga	ggtgcaccca	60
gacacgatct	acagtgtgga	ctggagccga	gatggaggcc	tcatttgtac	ctcctgccgt	120
gacaagcgcg	tgcgcatcat	cgagccccgc	aaaggcactg	tcgtagctga	gaaggaccgt	180
ccccacgagg	ggaccgggcc	cgtgcgtgca	gtgttcgtgt	cggaggggaa	gacccctgacc	240
acgggcttca	gccgcatgag	tgagcggcag	gtggcgctgt	gggacacaaa	gcacctggag	300
gagccgctgt	ccctgcagga	gctggacacc	agcagcggtg	tcctgctgcc	cttctttgac	360
cctgacacca	acatcgtcta	cctctgtggc	aagggtgaca	gctcaatccg	gtactttgag	420
atcacttcog	aggccctttt	cctgcactat	ctctccatgt	tcagttccaa	ggagtcccag	480
cggggcatgg	gctacatgcc	caaacgtggc	ctggagggtga	acaagtgtga	gatcgccagg	540
ttctacaagc	tgcacgagcg	gaggtgtgag	cccattgcca	tgacagtgcc	tcgaaagtcg	600
gacctgttcc	aggaggacct	gtaccacccc	accgcagggc	ccgaccctgc	cctcacggct	660
gaggagtggc	tggggggctcg	ggatgctggg	cccctcctca	tctccctcaa	ggatggctac	720
gtacccccaa	agagccggga	gctgagggtc	aaccggggcc	tggacaccgg	gcgcaggagg	780
gcagcaccag	aggccagtgg	cactcccagc	tcggatgccg	tgtctcggct	ggaggaggag	840
atgcggaagc	tccaggccac	ggtgcaggag	ctccagaagc	gcttggacag	gctggaggag	900
acagtccagg	ccaagtag					918

<210> 265

<211> 305

<212> PRT

<213> Homo Sapiens

<400> 265

Met Val Trp Asp Val Gly Thr Gly Ala Ala Met Leu Thr Leu Gly Pro
 1 5 10 15
 Glu Val His Pro Asp Thr Ile Tyr Ser Val Asp Trp Ser Arg Asp Gly
 20 25 30

Gly Leu Ile Cys Thr Ser Cys Arg Asp Lys Arg Val Arg Ile Ile Glu
 35 40 45
 Pro Arg Lys Gly Thr Val Val Ala Glu Lys Asp Arg Pro His Glu Gly
 50 55 60
 Thr Arg Pro Val Arg Ala Val Phe Val Ser Glu Gly Lys Ile Leu Thr
 65 70 75 80
 Thr Gly Phe Ser Arg Met Ser Glu Arg Gln Val Ala Leu Trp Asp Thr
 85 90 95
 Lys His Leu Glu Glu Pro Leu Ser Leu Gln Glu Leu Asp Thr Ser Ser
 100 105 110
 Gly Val Leu Leu Pro Phe Phe Asp Pro Asp Thr Asn Ile Val Tyr Leu
 115 120 125
 Cys Gly Lys Gly Asp Ser Ser Ile Arg Tyr Phe Glu Ile Thr Ser Glu
 130 135 140
 Ala Pro Phe Leu His Tyr Leu Ser Met Phe Ser Ser Lys Glu Ser Gln
 145 150 155 160
 Arg Gly Met Gly Tyr Met Pro Lys Arg Gly Leu Glu Val Asn Lys Cys
 165 170 175
 Glu Ile Ala Arg Phe Tyr Lys Leu His Glu Arg Arg Cys Glu Pro Ile
 180 185 190
 Ala Met Thr Val Pro Arg Lys Ser Asp Leu Phe Gln Glu Asp Leu Tyr
 195 200 205
 Pro Pro Thr Ala Gly Pro Asp Pro Ala Leu Thr Ala Glu Glu Trp Leu
 210 215 220
 Gly Gly Arg Asp Ala Gly Pro Leu Leu Ile Ser Leu Lys Asp Gly Tyr
 225 230 235 240
 Val Pro Pro Lys Ser Arg Glu Leu Arg Val Asn Arg Gly Leu Asp Thr
 245 250 255
 Gly Arg Arg Arg Ala Ala Pro Glu Ala Ser Gly Thr Pro Ser Ser Asp
 260 265 270
 Ala Val Ser Arg Leu Glu Glu Glu Met Arg Lys Leu Gln Ala Thr Val
 275 280 285
 Gln Glu Leu Gln Lys Arg Leu Asp Arg Leu Glu Glu Thr Val Gln Ala
 290 295 300
 Lys
 305

<210> 266

<211> 888

<212> DNA

<213> Homo Sapiens

<400> 266

atgctgacac	tgggcccaga	ggtgcaccca	gacacgatct	acagtgtgga	ctggagccga	60
gatggaggcc	tcatttgtac	ctcctgccgt	gacaagcgcg	tgcgcatcat	cgagccccgc	120
aaaggcactg	tcgtagctga	gaaggaccgt	ccccacgagg	ggacccggcc	cgtgcgtgca	180
gtgttcgtgt	cggaggggaa	gatcctgacc	acggggttca	gccgcatgag	tgagcggcag	240
gtggcgctgt	gggacacaaa	gcacctggag	gagccgctgt	ccctgcagga	gctggacacc	300
agcagcggtg	tcctgctgcc	cttctttgac	cctgacacca	acatcgtcta	cctctgtggc	360
aagggtgaca	gctcaatccg	gtactttgag	atcacttcg	aggccccctt	cctgcactat	420
ctctccatgt	tcagttccaa	ggagtcccag	cggggcatgg	gctacatgcc	caaacgtggc	480
ctggaggtga	acaagtgtga	gatcgccagg	ttctacaagc	tgacagagcg	gaggtgtgag	540
cccattgcca	tgacagtgcc	tcgaaagtgc	gacctgttcc	aggaggacct	gtacccaccc	600
accgcagggc	cgcaccctgc	cctcacggct	gaggagtggc	tggggggctc	ggatgctggg	660
ccctcctca	tctcctcaa	ggatggctac	gtaccccaa	agagccggga	gctgagggtc	720
aaccggggcc	tggacaccgg	gcgcaggagg	gcagcaccag	aggccagtgg	cactcccagc	780
tcggatgccg	tgtctcggct	ggaggaggag	atgcggaagc	tccaggccac	ggtgcaggag	840
ctccagaagc	gcttggacag	gctggaggag	acagtccagg	ccaagtag		888

<210> 267

<211> 295

<212> PRT

<213> Homo Sapiens

<400> 267

47

Met Leu Thr Leu Gly Pro Glu Val His Pro Asp Thr Ile Tyr Ser Val
 1 5 10 15
 Asp Trp Ser Arg Asp Gly Gly Leu Ile Cys Thr Ser Cys Arg Asp Lys
 20 25 30
 Arg Val Arg Ile Ile Glu Pro Arg Lys Gly Thr Val Val Ala Glu Lys
 35 40 45
 Asp Arg Pro His Glu Gly Thr Arg Pro Val Arg Ala Val Phe Val Ser
 50 55 60
 Glu Gly Lys Ile Leu Thr Thr Gly Phe Ser Arg Met Ser Glu Arg Gln
 65 70 75 80
 Val Ala Leu Trp Asp Thr Lys His Leu Glu Glu Pro Leu Ser Leu Gln
 85 90 95
 Glu Leu Asp Thr Ser Ser Gly Val Leu Leu Pro Phe Phe Asp Pro Asp
 100 105 110
 Thr Asn Ile Val Tyr Leu Cys Gly Lys Gly Asp Ser Ser Ile Arg Tyr
 115 120 125
 Phe Glu Ile Thr Ser Glu Ala Pro Phe Leu His Tyr Leu Ser Met Phe
 130 135 140
 Ser Ser Lys Glu Ser Gln Arg Gly Met Gly Tyr Met Pro Lys Arg Gly
 145 150 155 160
 Leu Glu Val Asn Lys Cys Glu Ile Ala Arg Phe Tyr Lys Leu His Glu
 165 170 175
 Arg Arg Cys Glu Pro Ile Ala Met Thr Val Pro Arg Lys Ser Asp Leu
 180 185 190
 Phe Gln Glu Asp Leu Tyr Pro Pro Thr Ala Gly Pro Asp Pro Ala Leu
 195 200 205
 Thr Ala Glu Glu Trp Leu Gly Gly Arg Asp Ala Gly Pro Leu Leu Ile
 210 215 220
 Ser Leu Lys Asp Gly Tyr Val Pro Pro Lys Ser Arg Glu Leu Arg Val
 225 230 235 240
 Asn Arg Gly Leu Asp Thr Gly Arg Arg Arg Ala Ala Pro Glu Ala Ser
 245 250 255
 Gly Thr Pro Ser Ser Asp Ala Val Ser Arg Leu Glu Glu Glu Met Arg
 260 265 270
 Lys Leu Gln Ala Thr Val Gln Glu Leu Gln Lys Arg Leu Asp Arg Leu
 275 280 285
 Glu Glu Thr Val Gln Ala Lys
 290 295

<210> 268
 <211> 75
 <212> DNA
 <213> Homo Sapiens

<400> 268
 atggaggcct catttggtacc tcttgccgtg acaagcgcgt gcgcacatc gagccccgca
 aaggcactgt cgttag

60
 75

<210> 269
 <211> 24
 <212> PRT
 <213> Homo Sapiens

<400> 269
 Met Glu Ala Ser Phe Val Pro Pro Ala Val Thr Ser Ala Cys Ala Ser
 1 5 10 15
 Ser Ser Pro Ala Lys Ala Leu Ser
 20

<210> 270
 <211> 663
 <212> DNA
 <213> Homo Sapiens

<400> 270

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atgagtgagc ggcaggtggc gctgtgggac acaaagcacc tggaggagcc gctgtccctg      60
caggagctgg acaccagcag cgggtgcctg ctgcccttct ttgacctga caccaacatc      120
gtctacctct gtggcaaggg tgacagctca atccgggtact ttgagatcac ttccgaggcc      180
cctttcctgc actatctctc catgttcagt tccaaggagt cccagcgggg catgggctac      240
atgccccaaac gtggcctgga ggtgaacaag tgtgagatcg ccagggttcta caagctgcac      300
gagcggagggt gtgagcccat tgccatgaca gtgcctcgaa agtcggacct gttccaggag      360
gacctgtacc caccaccgc agggcccgc cctgccctca cggctgagga gtggctgggg      420
ggtcgggatg ctggggccct cctcatctcc ctcaaggatg gctacgtacc cccaaagagc      480
cgggagctga gggtaaccg gggcctggac accgggcgca ggagggcagc accagaggcc      540
agtggcactc ccagctcgga tgccgtgtct cggctggagg aggagatgcg gaagctccag      600
gccacggtgc aggagctcca gaagcgcttg gacaggctgg aggagacagt ccaggccaag      660
tag

```

<210> 271

<211> 220

<212> PRT

<213> Homo Sapiens

<400> 271

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Met Ser Glu Arg Gln Val Ala Leu Trp Asp Thr Lys His Leu Glu Glu
 1          5          10          15
Pro Leu Ser Leu Gln Glu Leu Asp Thr Ser Ser Gly Val Leu Leu Pro
      20          25          30
Phe Phe Asp Pro Asp Thr Asn Ile Val Tyr Leu Cys Gly Lys Gly Asp
 35          40          45
Ser Ser Ile Arg Tyr Phe Glu Ile Thr Ser Glu Ala Pro Phe Leu His
 50          55          60
Tyr Leu Ser Met Phe Ser Ser Lys Glu Ser Gln Arg Gly Met Gly Tyr
 65          70          75          80
Met Pro Lys Arg Gly Leu Glu Val Asn Lys Cys Glu Ile Ala Arg Phe
      85          90          95
Tyr Lys Leu His Glu Arg Arg Cys Glu Pro Ile Ala Met Thr Val Pro
      100          105          110
Arg Lys Ser Asp Leu Phe Gln Glu Asp Leu Tyr Pro Pro Thr Ala Gly
      115          120          125
Pro Asp Pro Ala Leu Thr Ala Glu Glu Trp Leu Gly Gly Arg Asp Ala
      130          135          140
Gly Pro Leu Leu Ile Ser Leu Lys Asp Gly Tyr Val Pro Pro Lys Ser
      145          150          155          160
Arg Glu Leu Arg Val Asn Arg Gly Leu Asp Thr Gly Arg Arg Arg Ala
      165          170          175
Ala Pro Glu Ala Ser Gly Thr Pro Ser Ser Asp Ala Val Ser Arg Leu
      180          185          190
Glu Glu Glu Met Arg Lys Leu Gln Ala Thr Val Gln Glu Leu Gln Lys
      195          200          205
Arg Leu Asp Arg Leu Glu Thr Val Gln Ala Lys
      210          215          220

```

<210> 272

<211> 462

<212> DNA

<213> Homo Sapiens

<400> 272

```

atgttcagtt ccaaggagtc ccagcggggc atgggctaca tgcccaaacy tggcctggag      60
gtgaacaagt gtgagatcgc caggttctac aagctgcacg agcggagggtg tgagccatt      120
gcatgacagc tgcctcgaaa gtcggacctg ttccaggagg acctgtacct acccaccgca      180
gggcccagacc ctgccctcac ggctgaggag tggctggggg gtcgggatgc tgggcccctc      240
ctcatctccc tcaaggatgg ctacgtacct ccaaagagcc gggagctgag ggtcaaccgg      300
ggcctggaca cggggcgagc gagggcagca ccagaggcca gtggcactcc cagctcggat      360
gccgtgtctc ggctggagga ggagatgcgg aagctccagg ccacgggtgca ggagctccag      420
aagcgcttggt acaggctgga ggagacagtc caggccaagt ag      462

```

<210> 273

<211> 153

<212> PRT

<213> Homo Sapiens

<400> 273

```

Met Phe Ser Ser Lys Glu Ser Gln Arg Gly Met Gly Tyr Met Pro Lys
 1           5           10           15
Arg Gly Leu Glu Val Asn Lys Cys Glu Ile Ala Arg Phe Tyr Lys Leu
          20           25           30
His Glu Arg Arg Cys Glu Pro Ile Ala Met Thr Val Pro Arg Lys Ser
          35           40           45
Asp Leu Phe Gln Glu Asp Leu Tyr Pro Pro Thr Ala Gly Pro Asp Pro
          50           55           60
Ala Leu Thr Ala Glu Glu Trp Leu Gly Gly Arg Asp Ala Gly Pro Leu
          65           70           75           80
Leu Ile Ser Leu Lys Asp Gly Tyr Val Pro Pro Lys Ser Arg Glu Leu
          85           90           95
Arg Val Asn Arg Gly Leu Asp Thr Gly Arg Arg Arg Ala Ala Pro Glu
          100          105          110
Ala Ser Gly Thr Pro Ser Ser Asp Ala Val Ser Arg Leu Glu Glu Glu
          115          120          125
Met Arg Lys Leu Gln Ala Thr Val Gln Glu Leu Gln Lys Arg Leu Asp
          130          135          140
Arg Leu Glu Glu Thr Val Gln Ala Lys
          145          150

```

<210> 274

<211> 432

<212> DNA

<213> Homo Sapiens

<400> 274

```

atgggctaca tgcccaaacg tggcctggag gtgaacaagt gtgagatcgc caggttctac      60
aagctgcacg agcggagggtg tgagccatt gccatgacag tgcctcgaaa gtcggacctg      120
ttccaggagg acctgtaccc acccaccgca gggcccgacc ctgccctcac ggctgaggag      180
tggtggggg gtcgggatgc tgggccctc ctcattctccc tcaaggatgg ctacgtaccc      240
ccaaagagcc gggagctgag ggtcaaccgg ggctgggaca ccgggcgcag gagggcagca      300
ccagaggcca gtggcactcc cagctcggat gccgtgtctc ggctggagga ggagatgcgg      360
aagctccagg ccacggtgca ggagctccag aagcgcttgg acaggctgga ggagacagtc      420
caggccaagt ag                                     432

```

<210> 275

<211> 143

<212> PRT

<213> Homo Sapiens

<400> 275

```

Met Gly Tyr Met Pro Lys Arg Gly Leu Glu Val Asn Lys Cys Glu Ile
 1           5           10           15
Ala Arg Phe Tyr Lys Leu His Glu Arg Arg Cys Glu Pro Ile Ala Met
          20           25           30
Thr Val Pro Arg Lys Ser Asp Leu Phe Gln Glu Asp Leu Tyr Pro Pro
          35           40           45
Thr Ala Gly Pro Asp Pro Ala Leu Thr Ala Glu Glu Trp Leu Gly Gly
          50           55           60
Arg Asp Ala Gly Pro Leu Leu Ile Ser Leu Lys Asp Gly Tyr Val Pro
          65           70           75           80
Pro Lys Ser Arg Glu Leu Arg Val Asn Arg Gly Leu Asp Thr Gly Arg
          85           90           95
Arg Arg Ala Ala Pro Glu Ala Ser Gly Thr Pro Ser Ser Asp Ala Val
          100          105          110
Ser Arg Leu Glu Glu Glu Met Arg Lys Leu Gln Ala Thr Val Gln Glu
          115          120          125
Leu Gln Lys Arg Leu Asp Arg Leu Glu Glu Thr Val Gln Ala Lys
          130          135          140

```

<210> 276
 <211> 423
 <212> DNA
 <213> Homo Sapiens

<400> 276
 atgcccaaac gtggcctgga ggtgaacaag tgtgagatcg ccaggttcta caagctgcac 60
 gaggcgaggt gtgagcccat tgccatgaca gtgcctcgaa agtcggacct gttccaggag 120
 gacctgtacc caccaccgc agggcccgac cctgccctca cggctgagga gtggctgggg 180
 ggctcgggatg ctggggcccct cctcatctcc ctcaaggatg gctacgtacc cccaaagagc 240
 cgggagctga gggtaaccg gggcctggac accgggcgca ggagggcagc accagaggcc 300
 agtggcactc ccagctcgga tgccgtgtct cggctggagg aggagatgcg gaagctccag 360
 gccacggtgc aggagctcca gaagcgcttg gacaggctgg aggagacagt ccaggccaag 420
 tag 423

<210> 277
 <211> 140
 <212> PRT
 <213> Homo Sapiens

<400> 277
 Met Pro Lys Arg Gly Leu Glu Val Asn Lys Cys Glu Ile Ala Arg Phe
 1 5 10 15
 Tyr Lys Leu His Glu Arg Arg Cys Glu Pro Ile Ala Met Thr Val Pro
 20 25 30
 Arg Lys Ser Asp Leu Phe Gln Glu Asp Leu Tyr Pro Pro Thr Ala Gly
 35 40 45
 Pro Asp Pro Ala Leu Thr Ala Glu Glu Trp Leu Gly Gly Arg Asp Ala
 50 55 60
 Gly Pro Leu Leu Ile Ser Leu Lys Asp Gly Tyr Val Pro Pro Lys Ser
 65 70 75 80
 Arg Glu Leu Arg Val Asn Arg Gly Leu Asp Thr Gly Arg Arg Arg Ala
 85 90 95
 Ala Pro Glu Ala Ser Gly Thr Pro Ser Ser Asp Ala Val Ser Arg Leu
 100 105 110
 Glu Glu Glu Met Arg Lys Leu Gln Ala Thr Val Gln Glu Leu Gln Lys
 115 120 125
 Arg Leu Asp Arg Leu Glu Glu Thr Val Gln Ala Lys
 130 135 140

<210> 278
 <211> 339
 <212> DNA
 <213> Homo Sapiens

<400> 278
 atgacagtgc ctcgaaagtc ggacctgttc caggaggacc tgtacccacc caccgcaggg 60
 cccgaccctg ccctcacggc tgaggagtgg ctgggggggtc gggatgctgg gcccctcctc 120
 atctccctca aggatggcta cgtaccccca aagagccggg agctgagggt caaccggggc 180
 ctggacaccg ggcgcaggag ggcagcacca gaggccagtg gcactcccag ctcggtatgcc 240
 gtgtctcggc tggaggagga gatgcggaag ctccaggcca cgggtgcagga gctccagaag 300
 cgcttgagca ggctggagga gacagtccag gccaaagtag 339

<210> 279
 <211> 112
 <212> PRT
 <213> Homo Sapiens

<400> 279
 Met Thr Val Pro Arg Lys Ser Asp Leu Phe Gln Glu Asp Leu Tyr Pro
 1 5 10 15
 Pro Thr Ala Gly Pro Asp Pro Ala Leu Thr Ala Glu Glu Trp Leu Gly
 20 25 30
 Gly Arg Asp Ala Gly Pro Leu Leu Ile Ser Leu Lys Asp Gly Tyr Val
 35 40 45

Pro Pro Lys Ser Arg Glu Leu Arg Val Asn Arg Gly Leu Asp Thr Gly
 50 55 60
 Arg Arg Arg Ala Ala Pro Glu Ala Ser Gly Thr Pro Ser Ser Asp Ala
 65 70 75 80
 Val Ser Arg Leu Glu Glu Met Arg Lys Leu Gln Ala Thr Val Gln
 85 90 95
 Glu Leu Gln Lys Arg Leu Asp Arg Leu Glu Glu Thr Val Gln Ala Lys
 100 105 110

<210> 280
 <211> 63
 <212> DNA
 <213> Homo Sapiens

<400> 280
 atgctgggcc cctctcatc tccctcaagg atggctacgt acccccaaag agccgggagc 60
 tga 63

<210> 281
 <211> 20
 <212> PRT
 <213> Homo Sapiens

<400> 281
 Met Leu Gly Pro Ser Ser Ser Pro Ser Arg Met Ala Thr Tyr Pro Gln
 1 5 10 15
 Arg Ala Gly Ser
 20

<210> 282
 <211> 33
 <212> DNA
 <213> Homo Sapiens

<400> 282
 atggctacgt acccccaaag agccgggagc tga 33

<210> 283
 <211> 10
 <212> PRT
 <213> Homo Sapiens

<400> 283
 Met Ala Thr Tyr Pro Gln Arg Ala Gly Ser
 1 5 10

<210> 284
 <211> 238
 <212> DNA
 <213> Homo Sapiens

<400> 284
 atgccgtgtc tcggctggag gaggagatgc ggaagctcca ggccacggtg caggagctcc 60
 agaagcgctt ggacaggctg gaggagacag tccaggccaa gtagagcccc gcagggcctc 120
 cagcaggggc agccattcac acccatccac tcacctcca ttcccagcca catggcagag 180
 aaaaaaatca taataaaatg gctttatttt ctggtaaaaa aaaaaaaaaa ggccggcc 238

<210> 285
 <211> 79
 <212> PRT
 <213> Homo Sapiens

<400> 285
 Met Pro Cys Leu Gly Trp Arg Arg Arg Cys Gly Ser Ser Arg Pro Arg
 1 5 10 15

Cys Arg Ser Ser Arg Ser Ala Trp Thr Gly Trp Arg Arg Gln Ser Arg
 20 25 30
 Pro Ser Arg Ala Pro Gln Gly Leu Gln Gln Gly Gln Pro Phe Thr Pro
 35 40 45
 Ile His Ser Pro Pro Ile Pro Ser His Met Ala Glu Lys Lys Ile Ile
 50 55 60
 Ile Lys Trp Leu Tyr Phe Leu Val Lys Lys Lys Lys Lys Gly Gly
 65 70 75

<210> 286
 <211> 78
 <212> DNA
 <213> Homo Sapiens

<400> 286
 atgcggaagc tccaggccac ggtgcaggag ctccagaagc gcttggacag gctggaggag 60
 acagtccagg ccaagtag 78

<210> 287
 <211> 25
 <212> PRT
 <213> Homo Sapiens

<400> 287
 Met Arg Lys Leu Gln Ala Thr Val Gln Glu Leu Gln Lys Arg Leu Asp
 1 5 10 15
 Arg Leu Glu Glu Thr Val Gln Ala Lys
 20 25

<210> 288
 <211> 67
 <212> DNA
 <213> Homo Sapiens

<400> 288
 atggcagaga aaaaaatcat aataaaatgg ctttattttc tggtaaaaaa aaaaaaaag 60
 ggcggcc 67

<210> 289
 <211> 22
 <212> PRT
 <213> Homo Sapiens

<400> 289
 Met Ala Glu Lys Lys Ile Ile Ile Lys Trp Leu Tyr Phe Leu Val Lys
 1 5 10 15
 Lys Lys Lys Lys Gly Gly
 20

<210> 290
 <211> 41
 <212> DNA
 <213> Homo Sapiens

<400> 290
 atggctttat tttctggtaa aaaaaaaaaa aaagggcggc c 41

<210> 291
 <211> 13
 <212> PRT
 <213> Homo Sapiens

<400> 291
 Met Ala Leu Phe Ser Gly Lys Lys Lys Lys Lys Gly Arg
 1 5 10

<210> 292
 <211> 722
 <212> DNA
 <213> Homo Sapiens

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<400> 292
tcgacccacg cgtccgctct gccgcagcct gtgccgcgcg cgccctcctgg gaagagagga      60
agcgggagag gagccacgt ctccgtgcac ccaatatctc cagccgcgca gtcccgaaga      120
gtgtaagatg ttccgctgcg ccaagctcgc ctgcaccccc tctctgatec gagctggatc      180
cagagttgca tacagaccaa tttctgcata agtggtatct cgaccagagg ctagtaggac      240
tggagagggc tctacgggat ttaatggggc ccagaatggg gtgtctcagc taatccaaag      300
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ccttatcatt ggttatgccg gaaacccttc gctgaagcag cagctgttct catatgctat      480
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taattctgtg tatcttactg tgactccgaa aactgtagta ttggtgtcat gggaaatgtac      660
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gcaacagtag gagtggctgg ttctggtgct ggtattggaa cagtctttgg cagccttacc      300
attggttatg ccagaaaccc ttcgctgaag cagcagctgt tctcatatgc tatcctggga      360
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 <211> 142
 <212> PRT
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Pro Glu Ala Ser Arg Thr Gly Glu Gly Ser Thr Val Phe Asn Gly Ala
          35          40          45
Gln Asn Gly Val Ser Gln Leu Ile Gln Arg Glu Phe Gln Thr Ser Ala
          50          55          60
Ile Ser Arg Asp Ile Asp Thr Ala Ala Lys Phe Ile Gly Ala Gly Ala
          65          70          75          80
Ala Thr Val Gly Val Ala Gly Ser Gly Ala Gly Ile Gly Thr Val Phe
          85          90          95
Gly Ser Leu Ile Ile Gly Tyr Ala Arg Asn Pro Ser Leu Lys Gln Gln
          100         105         110
Leu Phe Ser Tyr Ala Ile Leu Gly Phe Ala Leu Ser Glu Ala Met Gly
          115         120         125
Leu Phe Cys Leu Met Val Ala Phe Leu Ile Leu Phe Ala Met
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 <213> Homo Sapiens

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<210> 296
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<212> PRT
<213> Homo Sapiens

<400> 296
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<210> 297
<211> 18
<212> DNA
<213> Homo Sapiens

<400> 297
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<210> 298
<211> 5
<212> PRT
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<400> 298
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<210> 299
<211> 21
<212> DNA
<213> Homo Sapiens

<400> 299
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<210> 300
<211> 6
<212> PRT
<213> Homo Sapiens

<400> 300
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<210> 301
<211> 51
<212> DNA
<213> Homo Sapiens

<400> 301
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<210> 302
<211> 16
<212> PRT
<213> Homo Sapiens

<400> 302
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<210> 303
<211> 51

<212> DNA
<213> Homo Sapiens

<400> 303
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<212> PRT
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<210> 305
<211> 33
<212> DNA
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<400> 305
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<210> 306
<211> 10
<212> PRT
<213> Homo Sapiens

<400> 306
Met Val Ala Phe Leu Ile Leu Phe Ala Met
1 5 10

<210> 307
<211> 51
<212> DNA
<213> Homo Sapiens

<400> 307
atgttggcat tcatattaat tacggatgta attctgtgta tcttactgtg a 51

<210> 308
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<210> 309
<211> 74
<212> DNA
<213> Homo Sapiens

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aaaaaagggc ggcc 74

<210> 310
<211> 24
<212> PRT
<213> Homo Sapiens

<400> 310
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56
10 15

1 5
Leu Lys Lys Lys Lys Lys Gly Arg
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<210> 311
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<212> DNA
<213> Homo Sapiens

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<210> 312
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<212> DNA
<213> Homo Sapiens

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<210> 313
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<210> 314
<211> 24
<212> DNA
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<400> 314
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<210> 315
<211> 7
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<400> 315
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1 5

<210> 316
<211> 18
<212> DNA
<213> Homo Sapiens

<400> 316
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<210> 317
<211> 5
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<400> 317

Met Ser Trp Arg Asp
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<210> 318

<211> 99

<212> DNA

<213> Homo Sapiens

<400> 318

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<211> 32

<212> PRT

<213> Homo Sapiens

<400> 319

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<210> 320

<211> 72

<212> DNA

<213> Homo Sapiens

<400> 320

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ttaggagcat ga 72

<210> 321

<211> 23

<212> PRT

<213> Homo Sapiens

<400> 321

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Lys Pro Ser Val Leu Gly Ala
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<210> 322

<211> 36

<212> DNA

<213> Homo Sapiens

<400> 322

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<210> 323

<211> 11

<212> PRT

<213> Homo Sapiens

<400> 323

Met Ser Leu His Lys Pro Ser Val Leu Gly Ala
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<210> 324

<211> 98

<212> DNA

<213> Homo Sapiens

<400> 324
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tttctagcag aaaaaaaaaa aaaaaaaaaa gggcggcc 98

<210> 325
<211> 32
<212> PRT
<213> Homo Sapiens

<400> 325
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<210> 326
<211> 1046
<212> DNA
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<400> 326
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ctagccacac cccacggga aacagcagtg attaaccttt agcaataaac gaaagttaa 180
ctaagctata ctaaccccag ggttggtcaa ttctgtgcca gccaccgcgg tcacacgatt 240
aaccacaagtc aatagaagcc ggcgtaaaga gtgttttaga tcaccccctc cccaataaag 300
ctaaaaactca cctgagttgt aaaaaactcc agttgacaca aaatagacta cgaaagtggc 360
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cttagcccta aacctcaaca gttaaatcaa caaaactgct cgccagaaca ctacgagcca 480
cagcttaaaa ctcaaaggac ctggcgggtgc ttcatacccc tctagaggag cctgttctgt 540
aatcgataaa ccccgatcaa cctcaccacc tcttgctcag cctatatacc gccatcttca 600
gcaaaccctg atgaaggcta caaagtaagc gcaagtaccc acgtaaagac gttaggtcaa 660
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<210> 327
<211> 24
<212> DNA
<213> Homo Sapiens

<400> 327
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<210> 328
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<210> 329
<211> 63
<212> DNA
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<210> 330
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<400> 330
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<210> 331
 <211> 108
 <212> DNA
 <213> Homo Sapiens

<400> 331
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<210> 332
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 <212> PRT
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<400> 332
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<210> 333
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 <212> DNA
 <213> Homo Sapiens

<400> 333
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<210> 334
 <211> 5
 <212> PRT
 <213> Homo Sapiens

<400> 334
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 1 5

<210> 335
 <211> 51
 <212> DNA
 <213> Homo Sapiens

<400> 335
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<210> 336
 <211> 16
 <212> PRT
 <213> Homo Sapiens

<400> 336
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PCT/US01/11655

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aaaaaaaaaaaa aaaaaaaaaa aaaagggcgg cc				152
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<213> Homo Sapiens				
<400> 342				
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Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys				
20 25 30				
Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys				
35 40 45				
Gly Arg				
50				

MICROORGANISMS

Optional Sheet in connection with the microorganism referred to on pages 116-117, lines 18-31 and 1-12 of the description *

A. IDENTIFICATION OF DEPOSIT *

Further deposits are identified on an additional sheet *

Name of depositary institution *

American Type Culture Collection

Address of depositary institution (including postal code and country) *

10801 University Blvd.
Manassas, VA 20110-2209
US

Date of deposit * March 16, 2000 Accession Number * PTA-1492

B. ADDITIONAL INDICATIONS * (leave blank if not applicable). This information is continued on a separate attached sheet

C. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE * (if the indications are not all designated States)

D. SEPARATE FURNISHING OF INDICATIONS * (leave blank if not applicable)

The indications listed below will be submitted to the International Bureau later * (Specify the general nature of the indications e.g., "Accession Number of Deposit")

E. ☐ This sheet was received with the International application when filed (to be checked by the receiving Office)

(Authorized Officer)

☐ The date of receipt (from the applicant) by the International Bureau *

was

(Authorized Officer)